

**A Combined Allylic Azide Rearrangement and Intramolecular
Schmidt Reaction – Discovery, Development, and Application**

By

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**A Combined Allylic Azide Rearrangement and Intramolecular
Schmidt Reaction – Discovery, Development, and Application**

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Abstract

The research presented herein describes synthetic applications of an allylic azide rearrangement, mainly focusing on its combination with the intramolecular Schmidt reaction to afford vinyl-substituted bicyclic lactams.

Undesired stereochemistry was obtained in the initial synthetic route to an advanced intermediate of natural product pinnaic acid, in which a home-made electrochemistry apparatus was involved in the key step to modify the tricyclic lactam. The combination of allylic azide rearrangement and intramolecular Schmidt reaction afforded the target with desired stereochemistry, and the synthesis of the cyclobutanone was achieved by an asymmetric [2+2] cycloaddition.

Prior to its combination with the intramolecular Schmidt reaction, the rearrangement of allylic azides was studied from different perspectives such as substrate, time, temperature, and Lewis acid. Next, the combined reaction was studied with the cyclohexanone-based allylic azide, whose stereochemical outcomes were rationalized by the conformational analysis and computational calculations. Different substituents on the cyclic ketone ring system were found to have different impacts on the diastereoselectivity. During this process, a chloro-Prins reaction was found as the major side-reaction, and carbocation-mediated allylic azide rearrangement was confirmed. Dihedral angle was utilized to explain why and in which cases the six-membered intermediate proceeds through chair or boat conformation for fused bicyclic system. This reaction was also utilized to produce twisted amides via cation- π interaction, along with the use of other by-products from different Lewis acids. The

utilization of this methodology to finish the total synthesis of alkaloid **205B** is underway.

Initial studies of the combination of allylic azide rearrangement and alkyne-azide cycloaddition were conducted. Also the reorganization of allylic azides was utilized to generate 2-azadiene species, which may undergo Diels-Alder reactions or electrocyclizations.

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CHAPTER 1

STUDIES TOWARDS THE SYNTHESIS OF PINNAIC ACID

1.1 Introduction

1.1.1 Pinnaic acid and related natural products

Pinnaic acid,¹ which represents a novel class of marine alkaloids characterized by a highly functionalized azaspiro[4,5]decane ring system, was isolated from the Okinawan bivalve *Pinna muricata* in 1996 by Uemura and co-workers. Its C17 stereochemistry was later determined through Danishefsky's total synthesis.^{2,3} However, its absolute configuration has not yet been confirmed due to the limited amount of naturally occurring sample. There are several related natural products with the same 6-aza-spiro[4,5]decane skeleton, such as tauropinnaic acid,¹ halichlorine,⁴ and pinnarine⁵ (Figure 1), which were isolated by the same group. Tauropinnaic acid was obtained together with pinnaic acid from the same plant. Halichlorine and pinnarine were isolated from the black marine sponge *Halichondria okadai* Kadota, in 1996 and 2011, respectively. The structure of pinnarine was further confirmed by its synthesis from pinnaic acid (Scheme 1).⁵ Thus, pinnarine and pinnaic acid have the same absolute configuration by the comparison of CD spectra of synthetic and natural products.

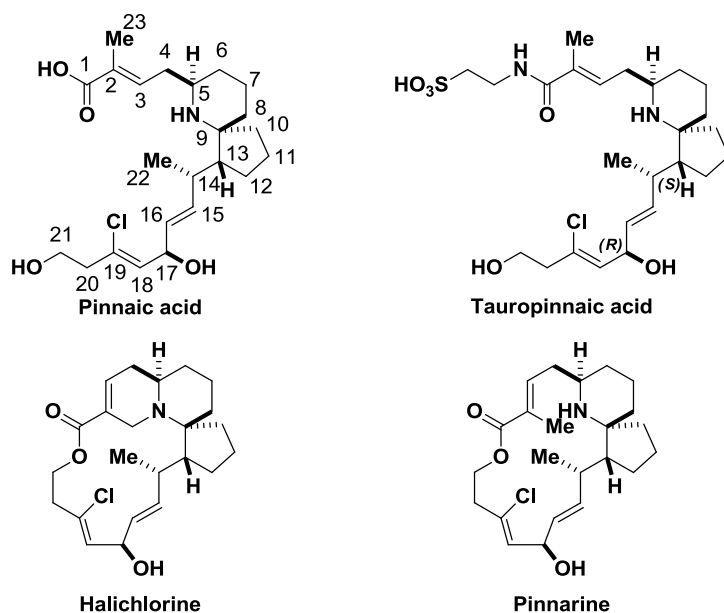
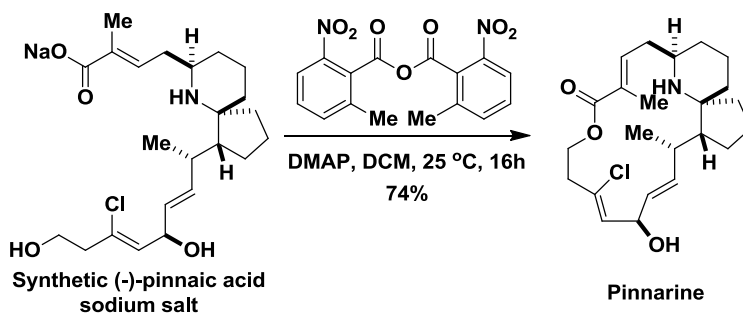


Figure 1. Pinnaic acid and related natural products.



Scheme 1. Conversion of (-)-pinnaic acid to pinnarine.

1.1.2 Biological activities

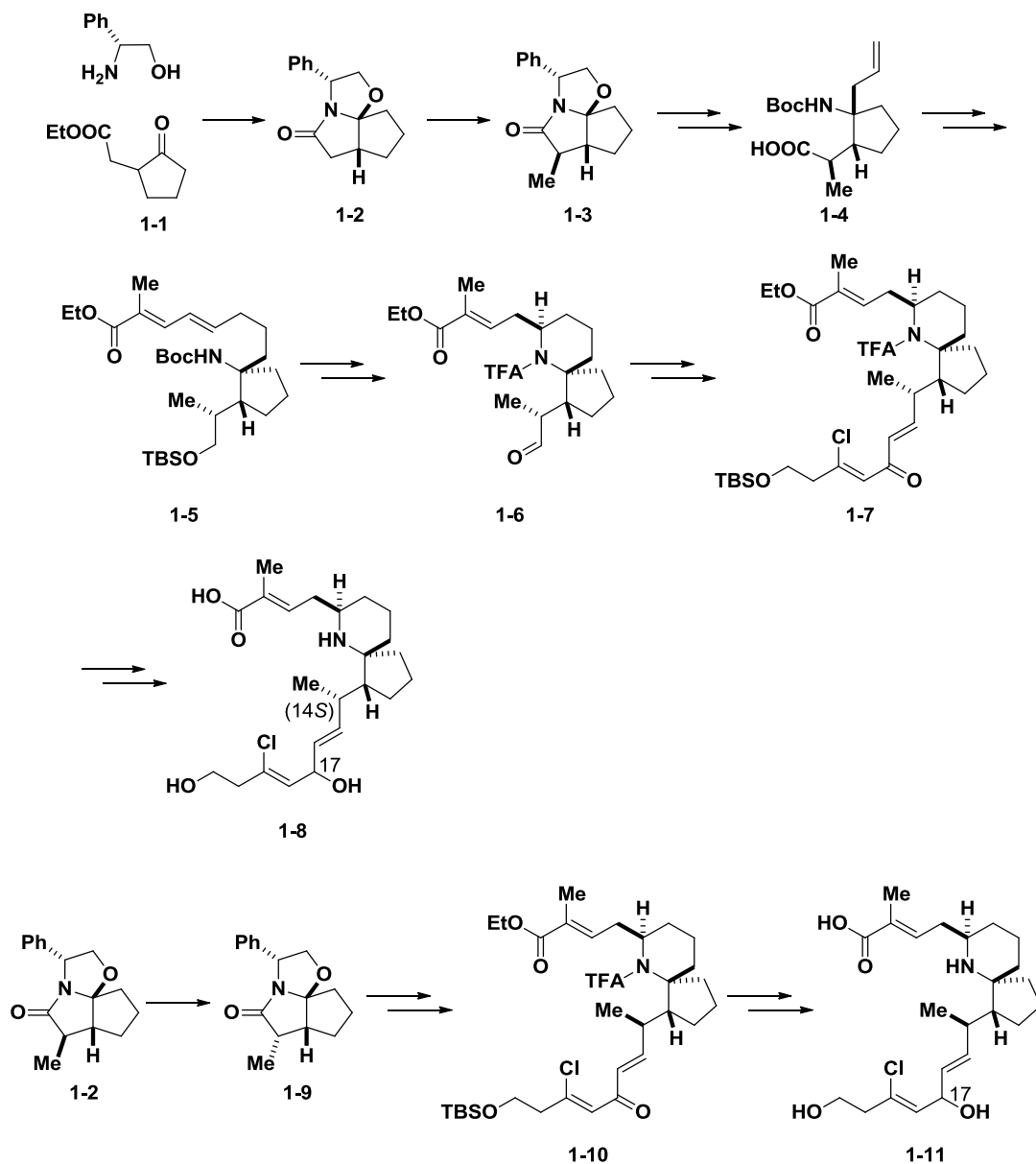
Pinnaic acid and tauropinnaic acid are specific inhibitors of a cytosolic 85 KDa phospholipase (cPLA_2) with an *in vitro* IC_{50} of 0.2 mM and 0.09 mM, respectively.¹ The cPLA_2 enzyme specifically recognizes the sn-2 acyl bond of phospholipids and hydrolyzes it releasing arachidonic acid, which can be further modified by cyclooxygenases into inflammatory mediators such as prostaglandins and leukotrienes.

Initially, halichlorine was reported to inhibit the induction of vascular cell-adhesive molecule-1 (VCAM-1) with an IC_{50} 7 $\mu\text{g/mL}$.⁴ More recently, halichlorine was found to inhibit lipopolysaccharide (LPS)-induced transcription factor nuclear factor- κB (NF- κB) and thus reduce the expression of VCAM-1 and monocyte adhesion to endothelial cells.⁶ It also inhibits L-type Ca^{2+} channels in vascular smooth muscle cells to reduce vascular contractions.⁷ Based on those discoveries, halichlorine could be applied to treat atherosclerosis and hypertension. No biological activity has been reported for pinnarine.

1.1.3 Total syntheses

Apart from these interesting biological activities, pinnaic acid's total synthesis is even more impressive for the synthetic chemistry community. To date there have been five reported total syntheses of pinnaic acid. They were reported by Danishefsky in 2001,^{2,3} Arimoto in 2003 and 2007,^{8,9} Heathcock in 2004,¹⁰ and Zhao in 2007.^{11,12} A review of this field appeared in 2005.¹³

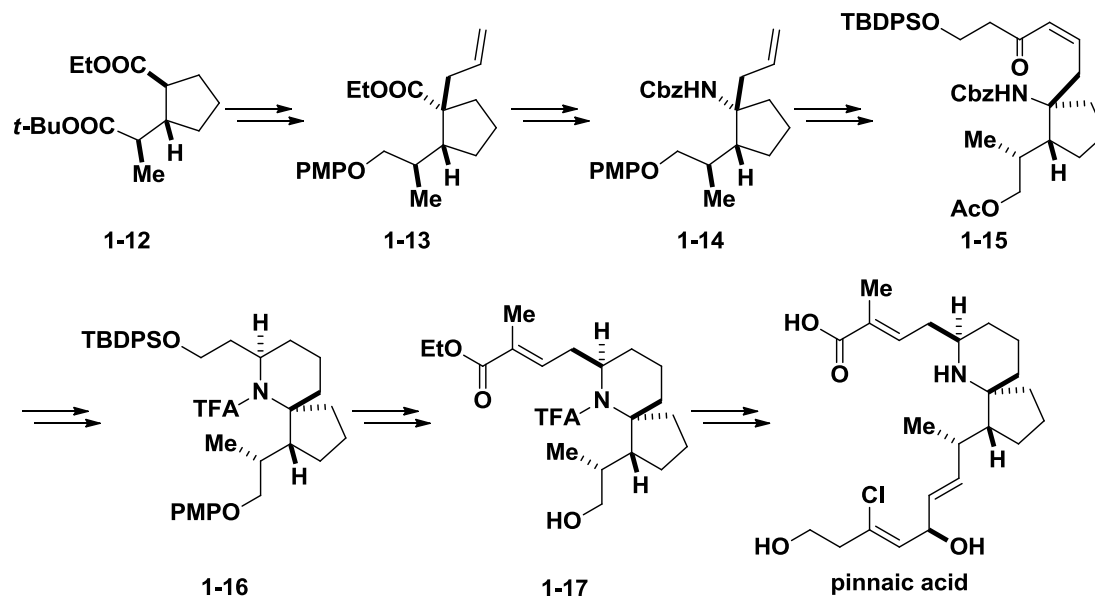
Danishefsky and co-workers started from (*R*)-(-)-phenylglycinol and methyl 2-(2-oxocyclopentyl)acetate (**1-1**) to construct tricyclic ring (**1-2**) with high diastereoselectivity, followed by methylation and allylation to afford aza-tertiary compound **1-4** (Scheme 2). After the aza-1,6 addition precursor **1-5** was obtained by the hydroboration and cross-coupling, aldehyde **1-6** afforded enone **1-7** via a Horner-Wadsworth-Emmons reaction (HWE reaction). The selective reduction of ketone **1-7** gave (14*S*,17*R*) and (14*S*,17*S*) diastereomers of pinnaic acid. The (14*R*,17*R*) and (14*R*,17*S*) diastereomers were obtained through the same strategy, starting from compound **1-9**. By a combination of total synthesis and chemical degradation of synthetic samples, pinnaic acid was assigned as the (14*S*,17*R*) diastereomer. The total synthesis of pinnaic acid was achieved in 19 linear steps from ketone **1-1**.



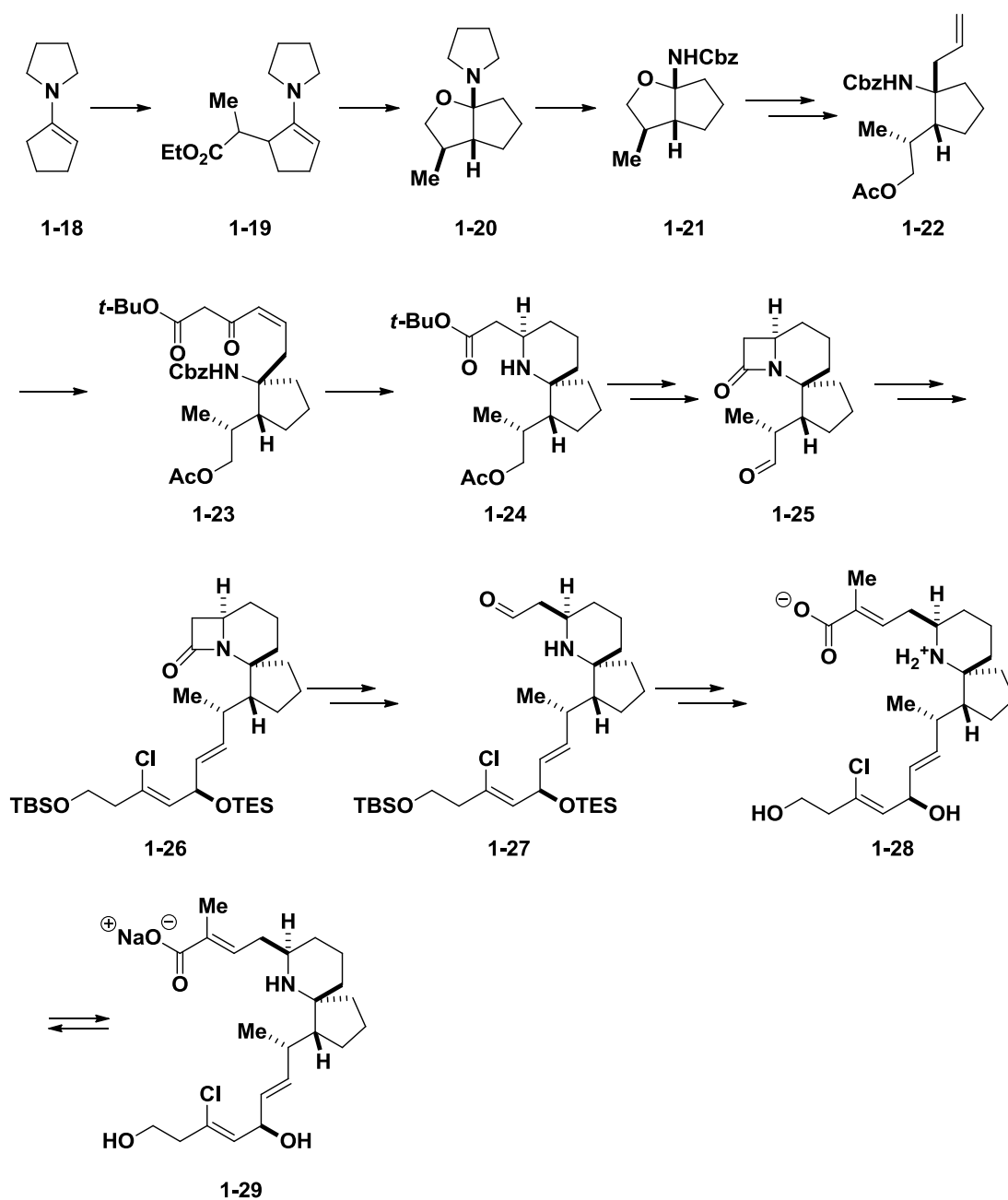
Scheme 2. Danishefsky and coworkers' synthetic route to pinnaic acid diastereomers.

In 2003, Arimato and co-workers used a Curtius rearrangement to set the aza-tertiary center in cyclopentane **1-14** (Scheme 3). The following ozonolysis and Horner-Wadsworth-Emmons reaction (HWE) gave the enone **1-15**, which was followed by the hydrogenation-cyclization to give spiro compound **1-16**. The second HWE reaction helped set up the

unsaturated ester sidechain of **1-17**. The total synthesis of pinnaic acid was accomplished following Danishefsky's strategy, in 19 linear steps from **1-12**.



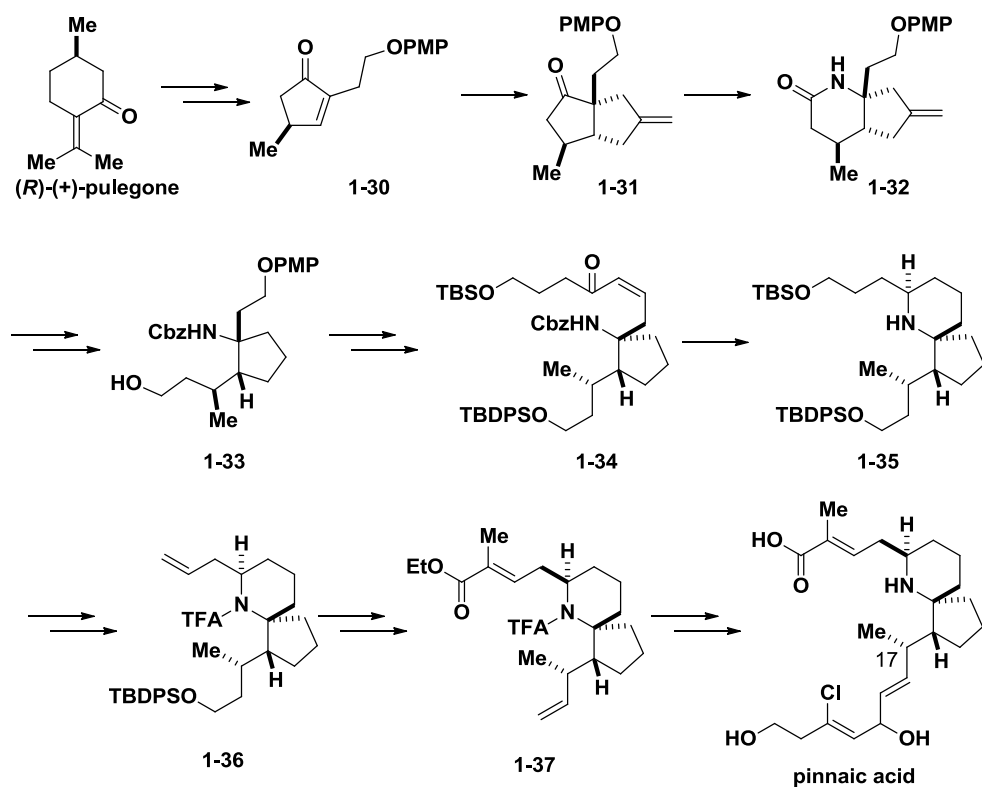
Scheme 3. Arimoto and coworkers' synthetic route to pinnaic acid.



Scheme 4. Heathcock and coworkers' synthetic route to pinnaic acid.

After Danishefsky and Arimoto's total syntheses, Heathcock used a different strategy to accomplish the total synthesis of pinnaic acid, taupinnaic acid, and halichlorine, from the common late-stage intermediate **1-27** (Scheme 4). Aza-tertiary compound **1-23** was obtained

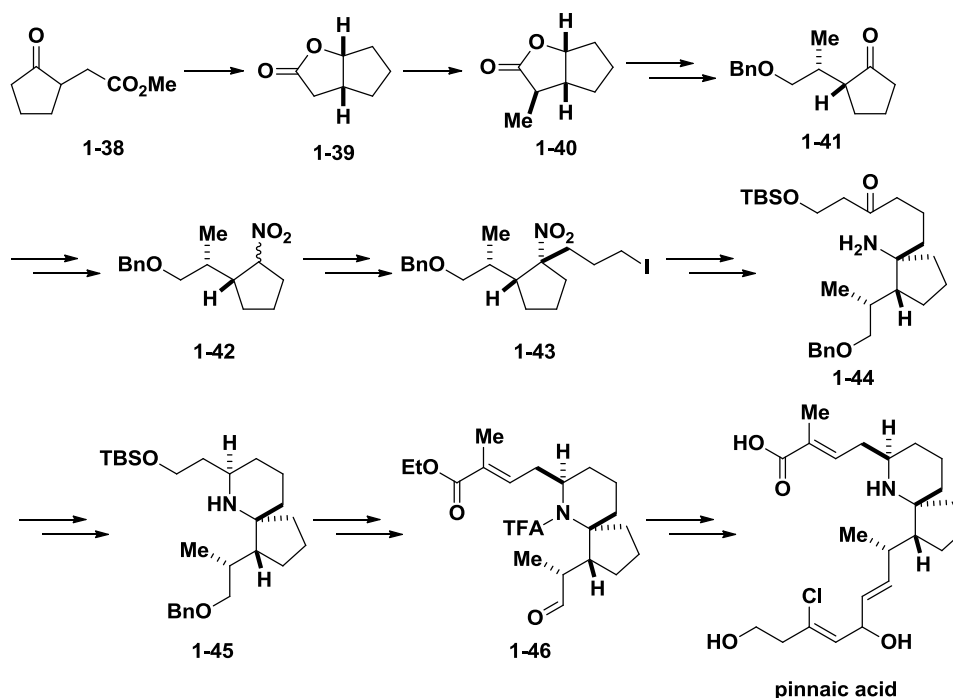
from 1-pyrrolidinyl-cyclopentene (**1-19**) using similar methodology as Danishefsky reported. The subsequent cross-metathesis and reductive amination then provided azaspiro[4,5]decane **1-24**, and β -lactam **1-25** was obtained by subsequent hydrolysis. The next HWE and asymmetric reduction afforded the bottom diol sidechain of **1-26**. The newly formed aldehyde **1-27** served as the key intermediate to all three natural products. The HWE reaction of **1-27** finished the end-game of pinnaic acid in 17 linear steps. Three forms of pinnaic acid, zwitterion **1-28**, conjugate base **1-29**, and its conjugate acid (not shown) were also studied. By comparing their spectral data, the originally isolated pinnaic acid was then most likely considered as the zwitterion, carboxylate, or a mixture of these two forms.



Scheme 5. Arimoto and coworkers' 2nd synthetic route to pinnaic acid.

In 2007, Arimoto reported their 2nd-generation total synthesis of pinnaic acid (Scheme 5). This time, they used a Beckmann rearrangement to set the aza-substituted

tertiary center of bicyclic lactam **1-32**. Bicyclic compound **1-35** was obtained, following their 1st generation strategy. Two consecutive cross-metathesis reactions finished installing the top ester and bottom diol sidechains, respectively. In this way, the total synthesis of pinnaic acid was finished in 25 linear steps from (*R*)-(+)-pulegone.



Scheme 6. Zhao and coworkers' synthetic route to pinnaic acid.

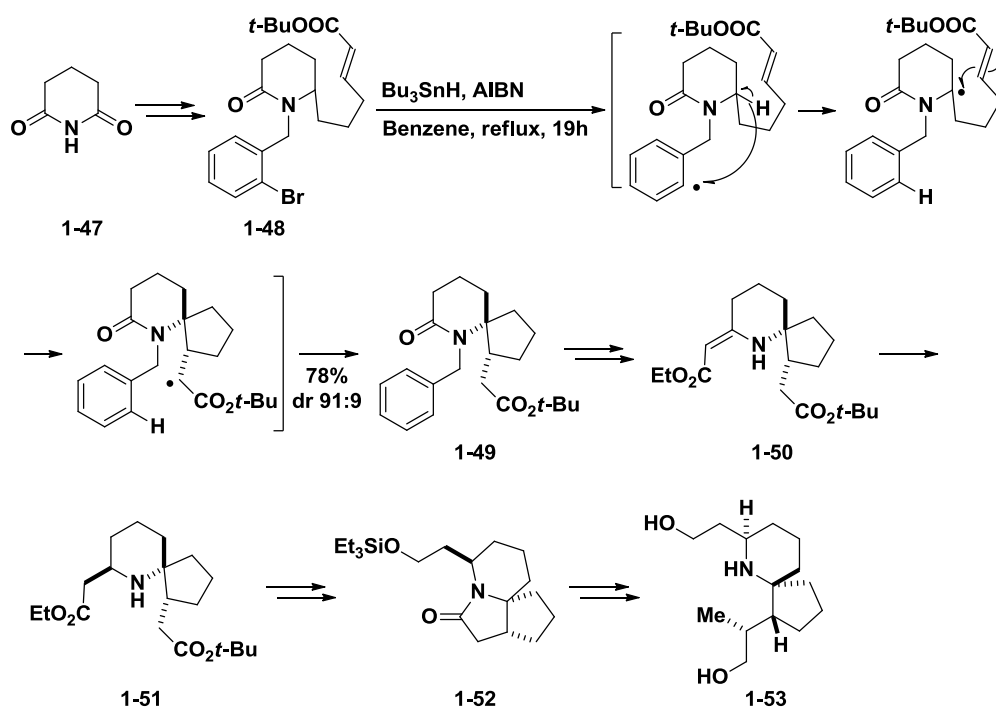
In the same year, Zhao used a retro-Nef reaction to convert ketone **1-41** to nitro group **1-42**, and the following alkylation finished the setup of the aza-substituted tertiary carbon (Scheme 6). Azaspiro[4,5]decane **1-45** was obtained from the reductive amination of **1-44**. Two separate HWE reactions then gave pinnaic acid in a total of 26 linear steps.

1.1.4 Synthetic routes towards azaspiro[4,5]decane core structure

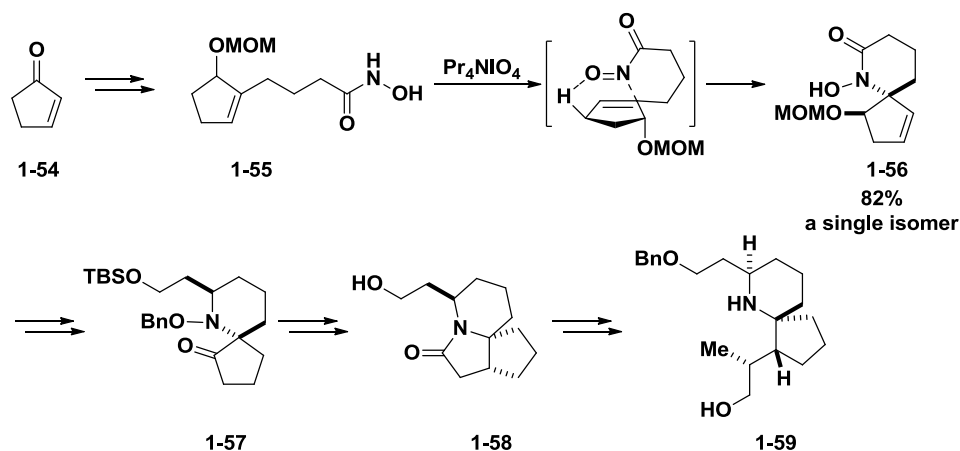
Besides its total synthesis, pinnaic acid's architectural core structure, 6-azaspiro[4,5]decane, has attracted additional attention from organic chemists. This probably

resulted from the existence of three common ways to end the total synthesis of pinnaic acid, either through HWE reaction, cross-metathesis, or a mixture of both. There are two important considerations for the synthesis of this core structure: (1) the introduction of the aza-tertiary center and (2) spiro[4,5] ring closure. In the reported total syntheses, the ring-closure is either through reductive amination or aza-michael addition. However, methods for the introduction of the aza-tertiary carbon center varied considerably, such as allylation of an in-situ generated acyliminium ion, Curtius rearrangement, Beckmann rearrangement, or α -alkylation of nitro group. Obviously, there are many other methods to construct the azaspiro[4,5]decane system, some of which are discussed below.

In 2003, Takasu and co-workers reported a cascade radical reaction involving radical translocation and cyclization reaction to achieve the construction of the azaspirobicyclic framework (Scheme 7).¹⁴ An aryl radical, generated from bromide **1-48**, cleaves an inactive C-H bond by [1,5] radical translocation to form α -aminyl radical, which is able to react successively with an intramolecular double bond to form the decane system **1-49**. Eschenmoser coupling reaction was utilized to afford the vinylogous amide **1-50**. Hydrogenation and lactamization afforded tricyclic lactam **1-52**.

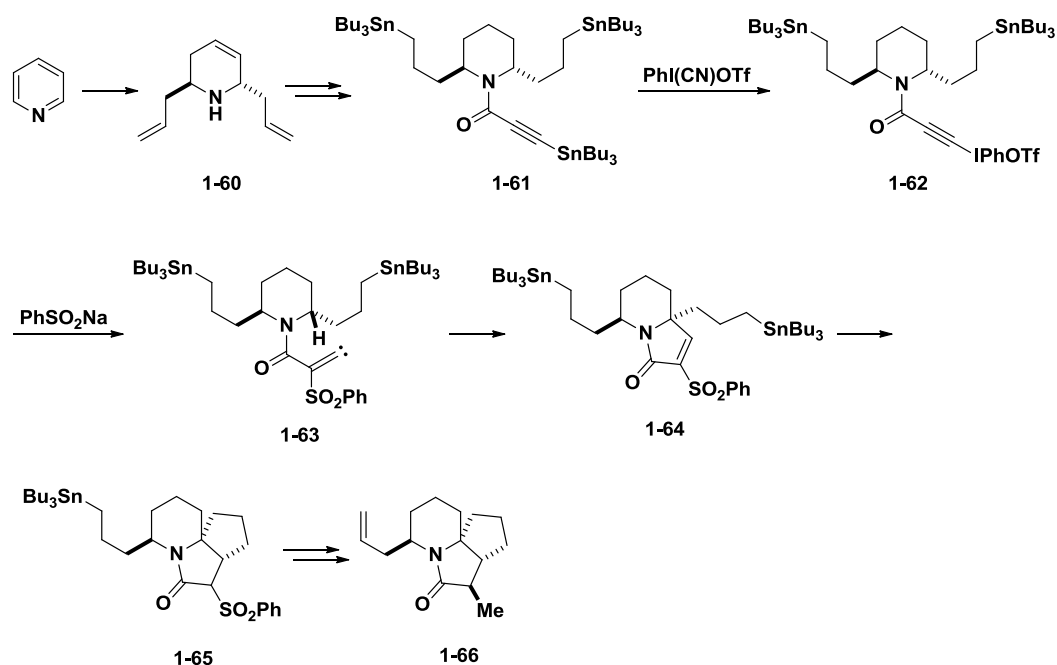


Scheme 7. Takasu and coworkers' synthetic route of core structure.



Scheme 8. Kibayashi and coworkers' synthetic route to the core structure.

The acylnitroso compound was generated from the oxidation of hydroxamic acid **1-55**, and the following intramolecular ene reaction proceeded to yield the spirocyclic lactam **1-56** (Scheme 8).^{15,16} Subsequent manipulations gave tricyclic lactam **1-58**.

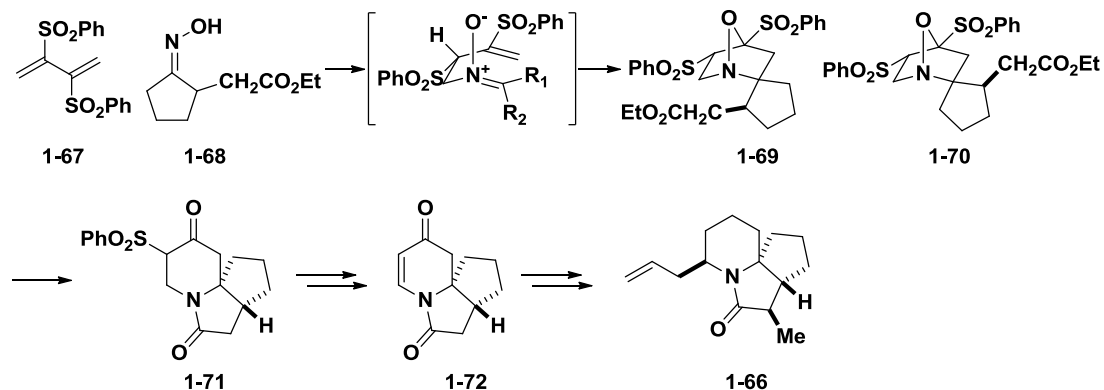


Scheme 9. Feldman and coworkers' synthetic route to the core structure.

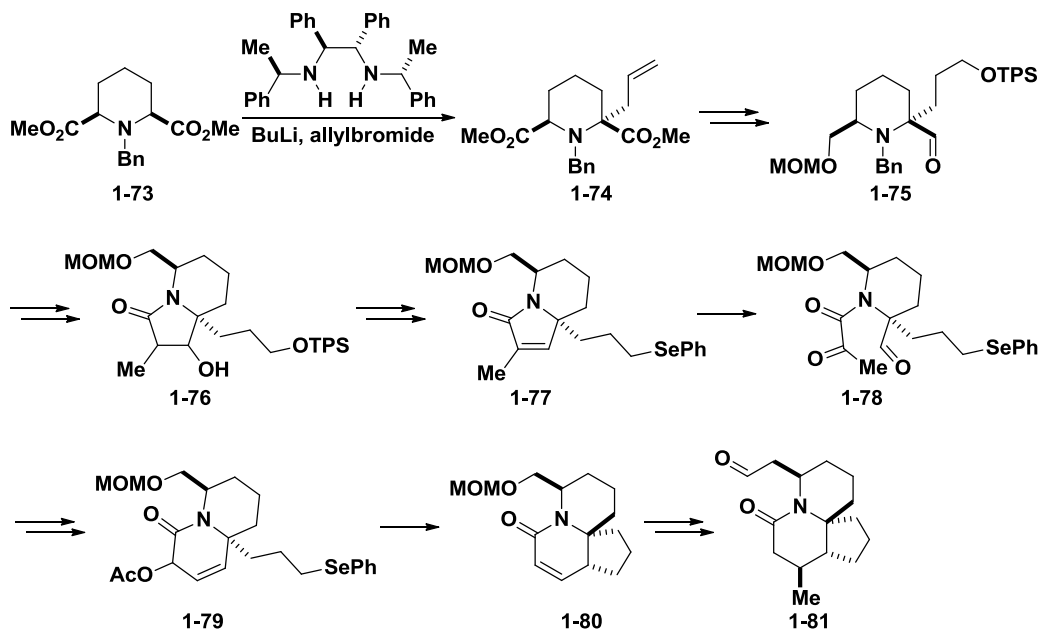
Alkynyliodonium salt chemistry was exploited to construct tricyclic lactam **1-66** by Feldman and co-workers in 2004 (Scheme 9).¹⁷ Prepared from stannane **1-61** using Stang's reagent, alkynyliodonium salt **1-62** formed alkylidene-carbene intermediate **1-63**, which can insert to the neighboring C-H bond with strict retention of configuration to form bicyclic lactam **1-64**. Two chemically identical C-Sn bonds were distinguished by magnesium bromide, due to the proximity of the enone portion to the quaternary propyl stannane appendage, to form tricyclic lactam **1-65**. The following transformations afforded key core structure **1-66**.

The same core structure was prepared later by Padwa and co-workers in 2010, using a well-established tandem conjugate addition/dipolar cycloaddition protocol developed in his group (Scheme 10).¹⁸ The conjugate addition of oxime **1-68** to 2,3-bisphenylsulfonyl-1,3-butadiene **1-67** formed a transient nitron intermediate, which underwent a dipolar cycloaddition to form bicyclic isoxazolidines **1-69** and **1-70**. Raney Ni reduction of the N-O

bond, subsequent desulfonylation, and cyclization furnished tricyclic lactam **1-71**. Lactam **1-66** was obtained by further transformations.



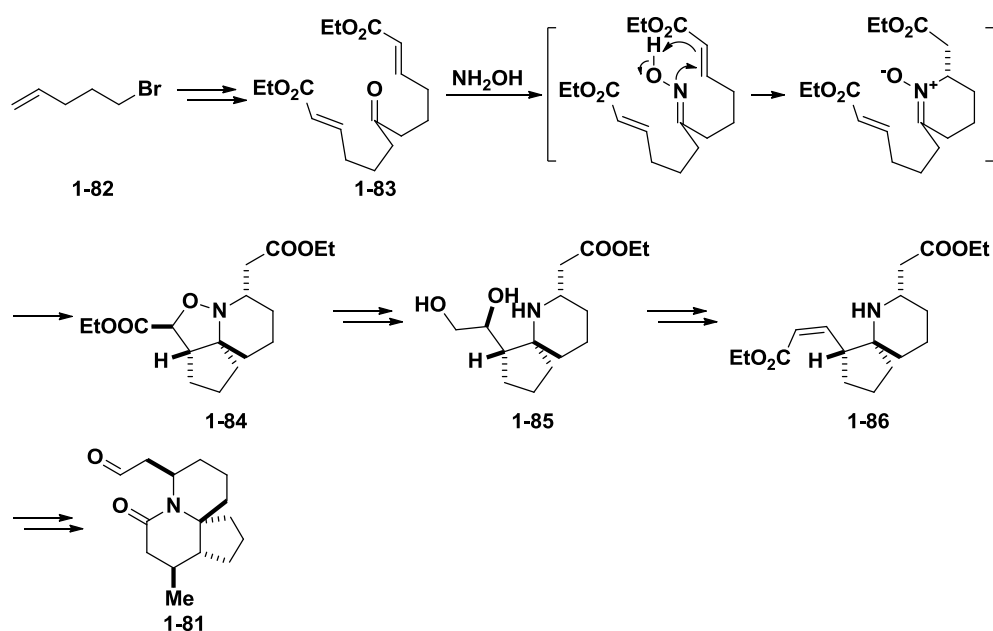
Scheme 10. Padwa and coworkers' synthetic route to the core structure.



Scheme 11. Clive and coworkers' synthetic route to the core structure.

Clive and co-workers used chiral base auxiliary assisted desymmetrization, which proved problematic upon scaling up, to give piperidine **1-74** (Scheme 11).^{19,20} The next transformations gave lactam **1-79**, which was cyclized to afford lactam **1-80**. Aldehyde **1-81** was obtained after several steps.

The same core structure was obtained recently by Stockman and co-workers (Scheme 12).²¹ The key step was an intramolecular ene/1,3 dipolar cycloaddition protocol to give the tricyclic ring of **1-84**. The subsequent reduction, oxidation, HWE reaction, and cyclization provided tricyclic lactam **1-81**.



Scheme 12. Stockman and coworkers' synthetic route to the core structure.

1.2 Evolution of our designs

Research in the Aubé laboratories has long focused on the synthesis of nitrogen-containing natural products using the intramolecular Schmidt reaction. The intramolecular Schmidt reaction has demonstrated its particular utility in the total synthesis of complex natural products, such as stenine,²² lepadiformines,²³ and alkaloid 223A.²⁴ As an alkaloid with a unique skeleton, pinnaic acid attracted our attention and we envisioned an efficient way to construct this core structure using an intramolecular Schmidt reaction. As described in the

introduction, the endgame strategies used by previous workers toward pinnaic acid are similar. Thus, we only focused on the synthesis of its core structure.

All the known tricyclic lactams used to synthesize pinnaic acid are listed in Figure 2. Most of them were prepared through multiple steps and only rarely in an enantiopure form. They can be classified in two categories: [5,6,6] and [5,5,6] tricyclic lactams, each having different side-chain appendages. For [5,5,6] tricyclic lactams, the methylated lactam could be easily obtained by LDA-mediated methylation with high diastereoselectivity as reported.¹⁶ Our goal was to develop an enantioselective synthetic route to one of the core structures listed in Figure 2.

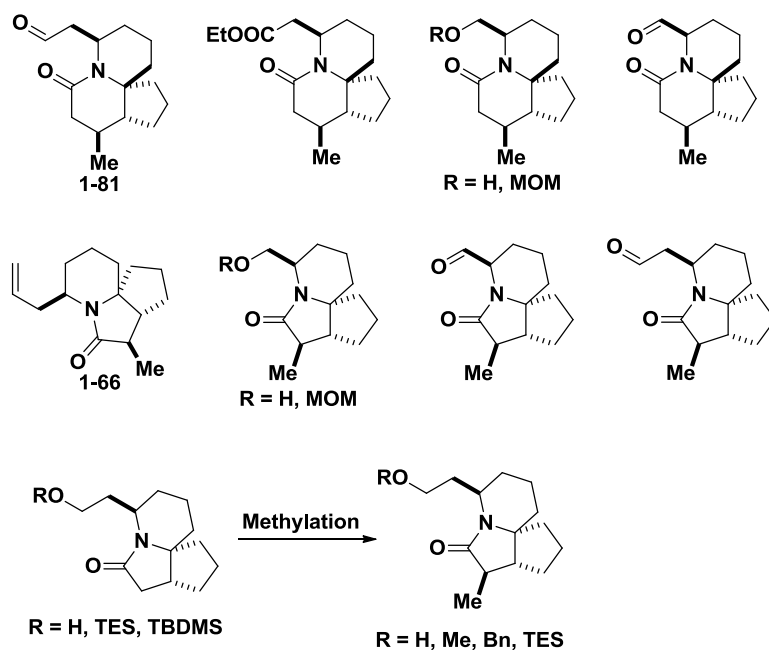
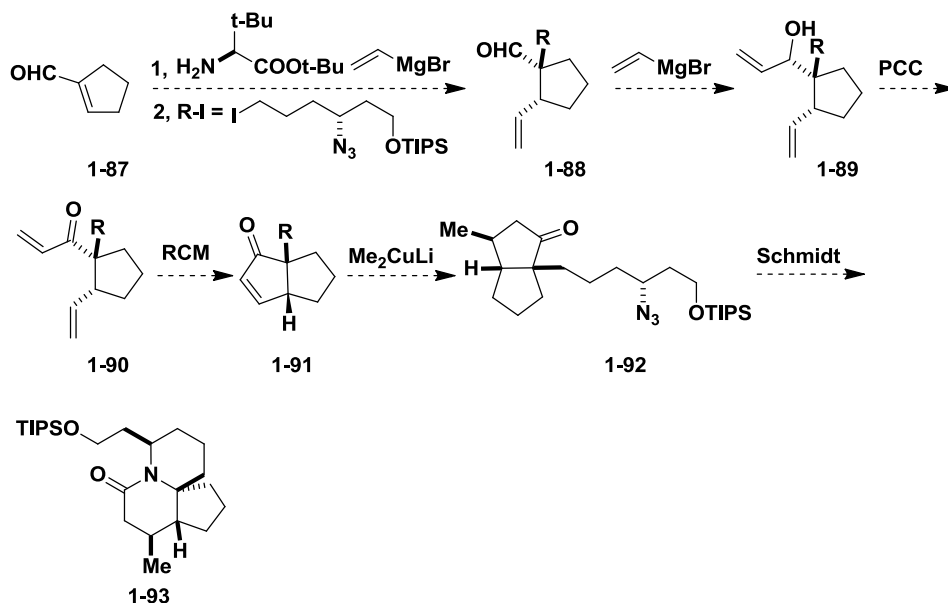


Figure 2. Known tricyclic lactam towards pinnaic acid.

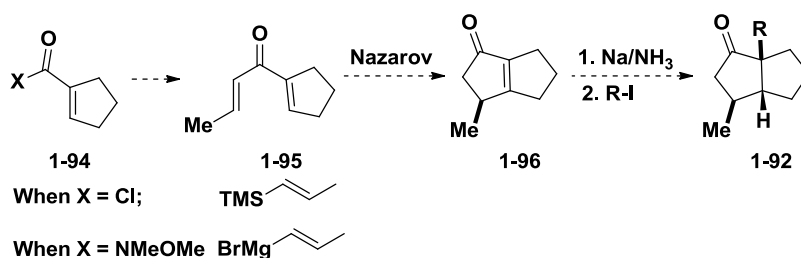
Initially, we focused on the synthesis of [5,6,6] tricyclic lactam **1-93**, the precursor of known lactam **1-81** (Scheme 13). Koga's elegant method would be used in the most important and challenging step, a conjugate addition of vinyl Grignard to the chiral imine derived from aldehyde **1-87**.²⁵ Trapping the enolate with alkyl halide could afford tertiary

aldehyde **1-88**. Unsaturated ketone **1-91** should be obtained by vinylation and subsequent ring-closing cross-metathesis. Conjugate addition by methyl cuprate could help set up *exo*-methyl group and the next intramolecular Schmidt should give the key lactam **1-93**.



Scheme 13. Initial design.

When we tried to prepare aldehyde **1-87** from compound **1-94** in the above design, we envisioned that an asymmetric Nazarov reaction followed by reductive alkylation could be used to get Schmidt precursor **1-92** (Scheme 14). When attempting to realize this strategy, there were some issues of this synthetic route: (1) compound **1-95** is volatile and formed in low yield and (2) Nazarov cyclization had the same problems. At the same time, we realized that we could utilize a [2+2] cycloaddition/Schmidt strategy, and thus we stopped our pursuits of this route in Scheme 14.



Scheme 14. Initial synthetic route.

The [2+2] cycloaddition/Schmidt strategy was based on [5,5,6] tricyclic lactam **1-66** (Figure 3). Fortunately, a wonderful electrochemistry apparatus was developed by Dr. Kevin Frankowski around that time after his study with Prof. Kevin Moeller's group at Washington University in Saint Louis. This method could functionalize the potential Schmidt product **1-99** to form an iminium ion **1-98**, followed by the allylation and methylation to afford known core structure **1-66** (Figure 3). The Schmidt precursor **1-100** is easily prepared from known cyclobutanone **1-101**, which can be prepared through two methods: ketene and keteneiminium-mediated [2+2] cycloadditions. Ghosez and co-workers previously developed chiral amide-assisted [2+2] cycloaddition to afford enantiopure cyclobutanones.²⁶ We envisioned that the enantiopure form of **1-101** could be prepared through this methodology.

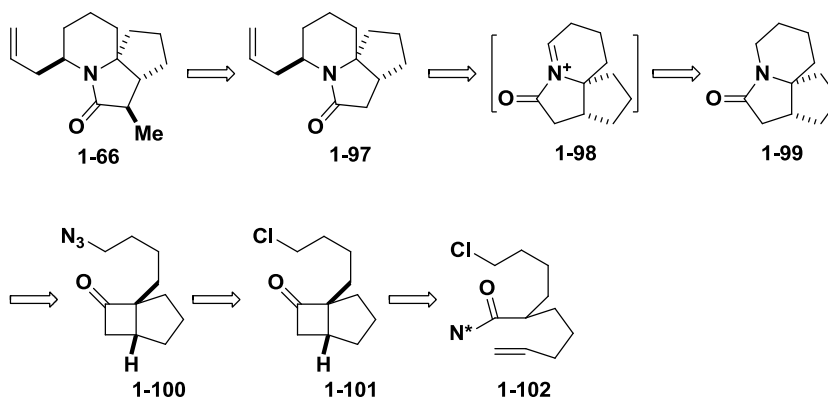


Figure 3. Electrochemistry-mediated retrosynthetic analysis.

In the above design, the allyl group and methyl group would be introduced at a late stage. In our ideal design, the side chain could be introduced in the early stage via an allylic azide rearrangement/Schmidt cascade reaction. We also considered the possibility of the introduction of the methyl group in the early stage.

Alternatively, known tricyclic lactam **1-103** could be synthesized from **1-104** by hydroboration/oxidation (Figure 4). In this approach, one of four interconverting allylic azide isomers could proceed to the intramolecular Schmidt reaction to generate lactam **1-104**. The allylic azide rearrangement is facile at room temperature and its major isomer is azide **1-106**, which can be prepared by the azide displacement of bromide **1-107**.

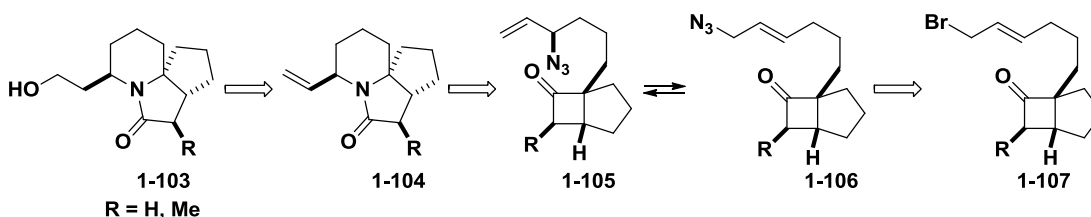


Figure 4. Allylic azide rearrangement/Schmidt mediated retrosynthetic analysis.

The next problem was to find an efficient way to prepare this bromide. The ideal would be to prepare methylated cyclobutanone derivative **1-107** (R=Me) (Figure 5). A common method to prepare such allylic bromides is through radical-mediated allylic bromination using NBS. There are two types of substrates suitable for this radical reaction. One is the internal olefin **1-108** (or **1-109**), and the other terminal olefin **1-111**. Cyclobutanone **1-108** might be prepared from C_2 -symmetric amide **1-113** by chiral amide-assisted asymmetric [2+2] cycloaddition via a keteniminium ion intermediate although no related compounds were reported. Even though the methyl group on the olefin affects this cycloaddition, methylated and non-methylated olefins can be present in one molecule (such as **1-114**) and compete to produce either cyclobutanone **1-109** or **1-110**. This also helps us to

more fully understand the [2+2] cycloaddition. The known compound **1-111** is prepared by a competitive [2+2] cycloaddition via a ketene intermediate preferentially reacting with the closer olefin.²⁷ We also tried to get its enantiopure form through the chiral amide-assisted asymmetric [2+2] cycloaddition from **1-115**.

Another method to prepare allylic bromide **1-107** (R=H) is cross metathesis of **1-112** with allylbromide. Cyclobutanone **1-112** is also known, but its asymmetric synthesis had not been reported. We also envisioned preparing its enantiopure form from C_2 -symmetric amide **1-116**.

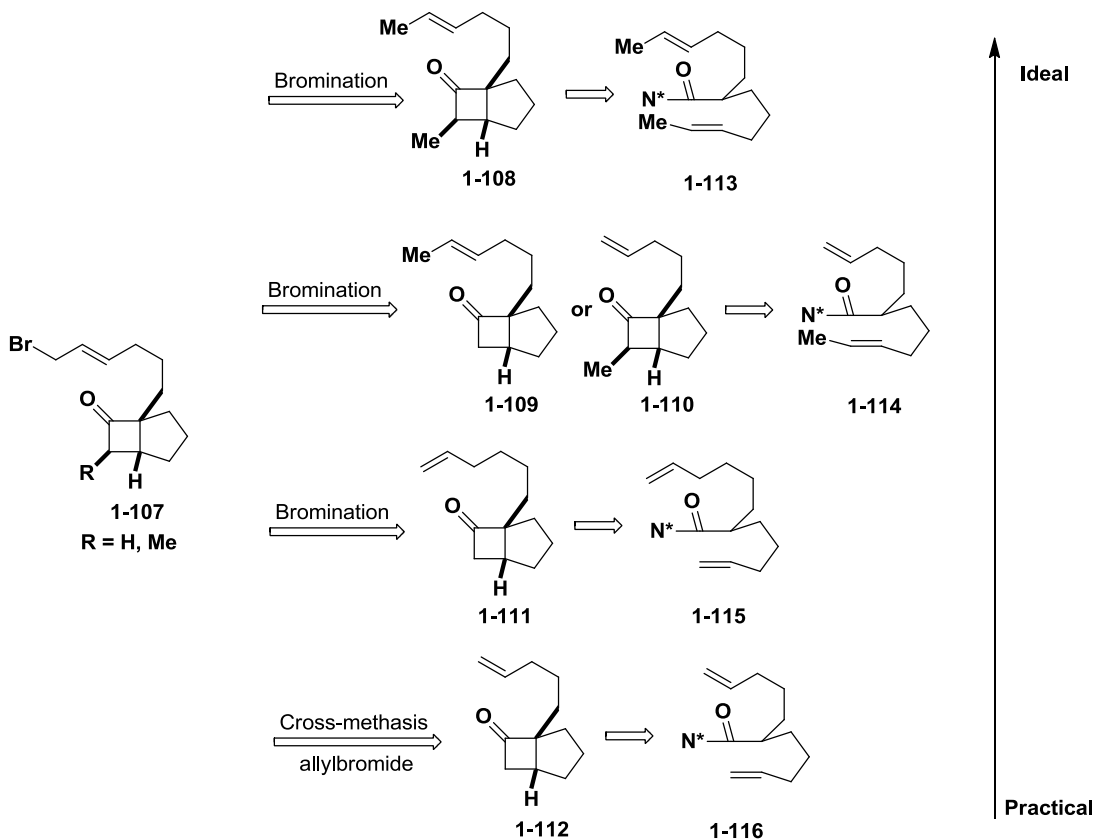


Figure 5. Possible methods for the preparation of allylic azide.

1.3 [2+2] cycloaddition

1.3.1 Mechanistic discussions

The [2+2] cycloaddition, which involves two olefins to form cyclobutane derivatives, is one of the most powerful pericyclic reactions. Based on the frontier molecule orbital (FMO) theory, the HOMO of one ethylene and the LUMO of another cannot approach each other in the same face (suprafacial-suprafacial interaction) due to the unmatched phasing, and thus no constructive interaction can occur (Figure 6a). But, if the interaction mode of one ethylene is changed from suprafacial to antarafacial, this cycloaddition is thermally allowed, and designated as $[\pi 2_s + \pi 2_a]$ (Figure 6b). However, this construction is difficult to achieve in practice due to the existing steric interaction between the substituents of one alkene and the molecular plane of another.

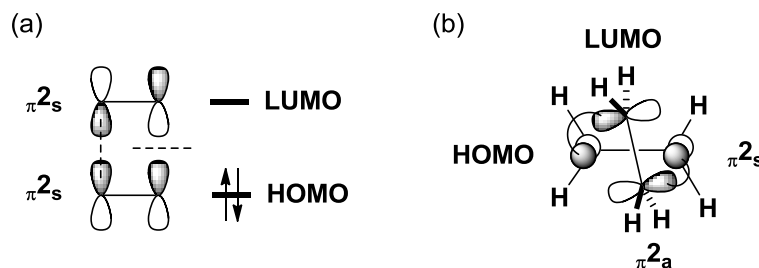


Figure 6. [2+2] cycloaddition. (a) Face-to-face interaction. (b) Crossed approach.

Although this kind of hindrance is much less for cumulene systems in comparison to those of normal alkenes, not all of them can easily undergo [2+2] cycloaddition at or below room temperature. There are three well-known types of cumulene systems: allenes, ketenes, and keteniminium ions. Although there are many reported [2+2] cycloaddition reactions of allenes to afford cyclobutane and cyclobutene derivatives under thermal conditions (over 200 °C), most are considered to involve diradical intermediates in a stepwise mechanism instead of a concerted process, as have been thoroughly reviewed.²⁸

In contrast, ketenes and their nitrogen analogs, keteniminium ions, have been much more common substrates for [2+2] cycloadditions since the beginning of the last century. There are some controversies over the detailed mechanism of the [2+2] cycloaddition between ketenes and alkenes although it is generally considered a concerted process.²⁹ Initially, this reaction was described as a $[\pi 2_s + \pi 2_a]$ cycloaddition by Woodward and Hoffmann, suprafacial on the alkene and antarafacial on the ketene because of steric hindrance (Figure 8A). However, it is insufficient to consider the molecular orbitals of ketene as merely two orthogonal π systems.³⁰ Bottoni and co-workers used MCSCF studies to calculate the π orbitals of ketene and its relevance to alkenes, and found that there is some mixing of orbitals with C-H bonds and the lone pairs of oxygen (Figure 7).³¹ They also compared three different interactions between ketenes and alkenes: supra-antara, parallel, and perpendicular approaches. Their results supported this idea that the ethylene attacks the middle carbon of ketene from a plane parallel to the ketene plane. A similar result was found by Houk and Wang in the same year through ab initio molecular orbital calculations. They indicated electrophilic interaction of the central carbon of ketene using in-plane $\pi_{C=O^*}$ orbital with $\pi_{C=C}$ orbital of the olefin in an asynchronous process, and the next cycloaddition resulting from the perpendicular addition of C-C HOMO orbital of ketene to alkenes (Figure 8B).³² This process is designated as $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ cycloaddition.³³

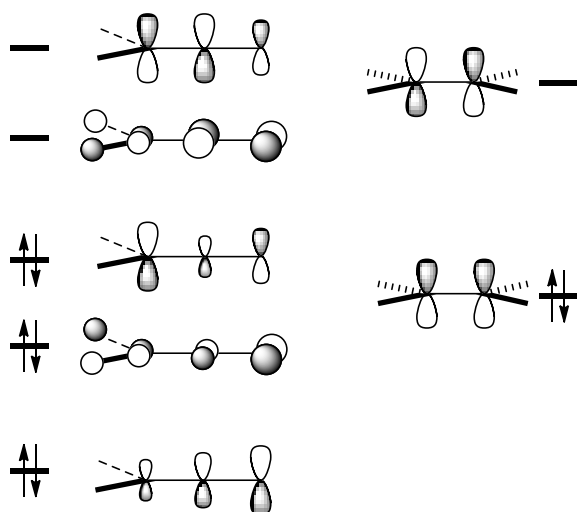


Figure 7. π orbitals of ketene and ethylene.

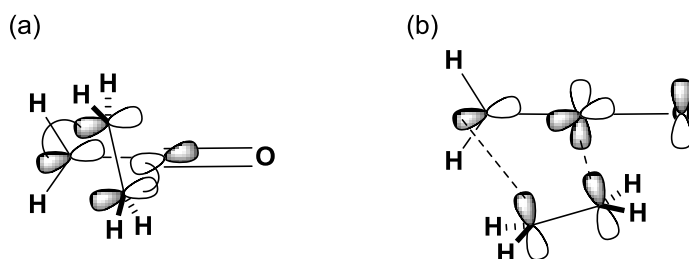
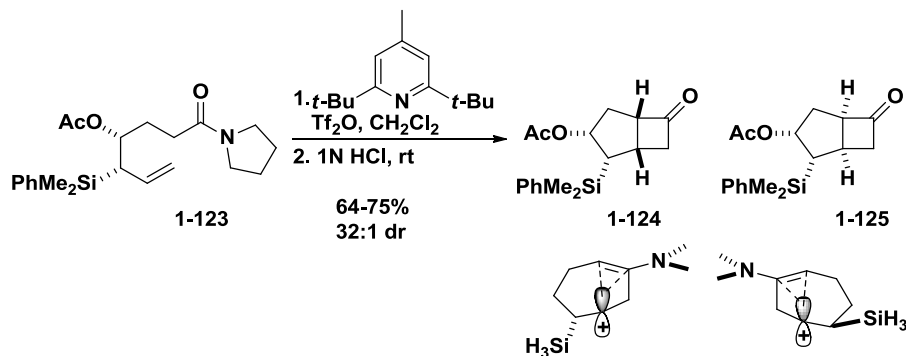


Figure 8. [2+2] cycloaddition between ketene and alkene. (a) Woodward and Hoffmann's approach. (b) Houk and Wang's approach.

In contrast to many computational studies of [2+2] cycloaddition between ketene and alkene, only two articles reported on [2+2] cycloadditions between keteniminium ions and alkene until now. Importantly, their results are similar to those reported for ketenes. In 1999, Ghosez, Houk and coworkers used a silyl group as the stereodirecting group to achieve high diastereoselectivity in the [2+2] cycloaddition (Scheme 15).³⁴ Through ab initio and density functional theory methods, they found the electrophilic in-plane attack of the middle carbon of keteniminium ion to the alkene to form two possible bridged enamine cations, one of which is stabilized by silicon, whereas the other is not. Steric hindrance could also be another reason for high diastereoselectivity, with the big silyl group capable of blocking the

electrophilic attack of the keteniminium ion to form the minor isomer. Similar results were obtained by Fang and coworkers.³⁵



Scheme 15. Silicon-involved intramolecular [2+2] cycloaddition of keteniminium ion.

1.3.2 [2+2] cycloaddition reaction

In this section, only intramolecular [2+2] cycloadditions related to this project are discussed.

Intramolecular [2+2] cycloaddition reactions of ketene with alkene are similar to intermolecular [2+2] cycloaddition, in which the addition of alkene to ketene has two pathways: *fused* and *crossed* pathways to form compounds **1-127** and **1-128**, respectively (Figure 9). This regioselectivity is determined by the electronic pattern of alkenes. If the internal carbon of the alkene is more substituted, i.e. making the terminal carbon of alkene more nucleophilic, the [n,2,0] bicyclic cyclobutanones **1-127** are produced via the *fused* pathway. Otherwise, when the terminal carbon of alkene is more substituted, i.e., making the internal carbon of alkene more nucleophilic, the [n,1,1] bicyclic cyclobutanones **1-128** are obtained via a *crossed* pathway.

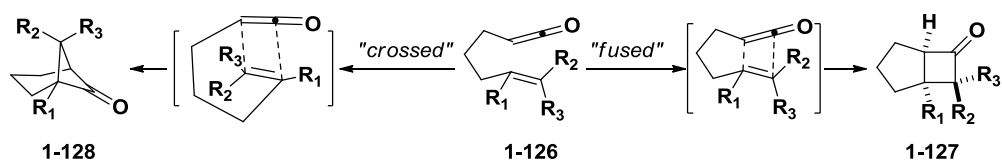


Figure 9. Different pathways for intramolecular [2+2] cycloadditions.

Keteniminium ions are isoelectronic to ketenes, but they lack one free electron pair as on the oxygen, which makes ketenes have the 1,2-dipolar character, although both have the vinyl cation character (Figure 10). Thus, this kind of difference imparts many advantages to keteniminium ions over ketenes in the [2+2] cycloaddition, such as a lesser tendency to undergo dimerization or polymerization reactions, ready availability, and being easy to handle. The conditions associated with this cycloaddition reactions are mild and reactions often occur in the excellent yields. The chemistry of keteniminium ions was reviewed in late 1980s³⁶ and last year.³⁷

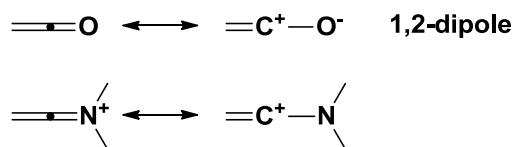
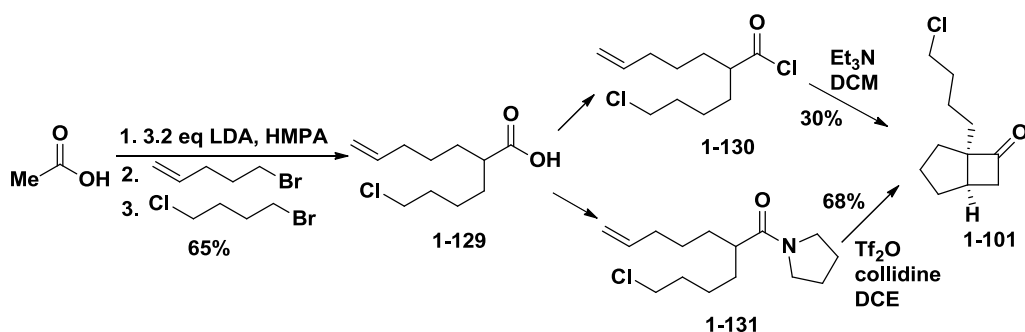


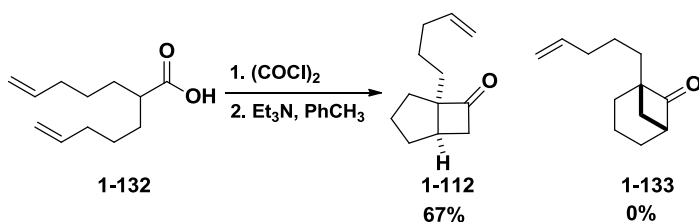
Figure 10. Electronic comparison of ketenes and keteniminium ions.

In 1995, Dowd and coworkers reported the synthesis of compound **1-101** and its free radical ring expansion (Scheme 16).³⁸ First, chloride **1-129** was prepared using a one-pot dialkylation of the dianion of acetic acid. Following that, [2+2] cycloadditions were carried out via both ketene and keteniminium ion intermediates. The better yield was obtained from the keteniminium salt.



Scheme 16. Synthetic routes of compound **1-101**.

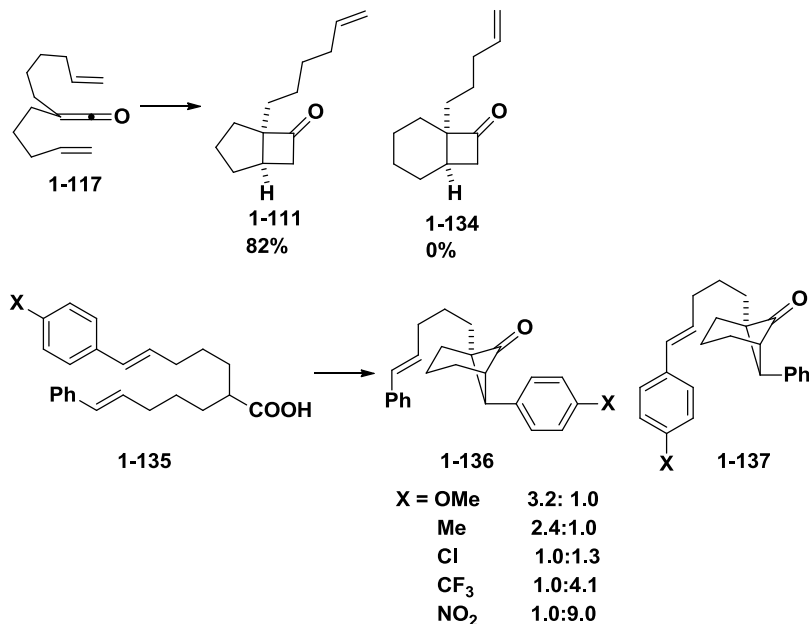
The preparation of compound **1-112** was reported by Snider and coworkers (Scheme 17).³⁹ Importantly, only *fused* product **1-112** was obtained without any observation of *crossed* product **1-133**. Furthermore, the substrate **1-132** possessed σ -symmetry, simplifying this [2+2] cycloaddition.



Scheme 17. Preparation of compound **1-112**.

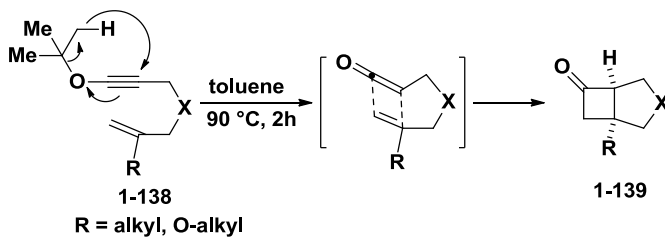
In 2005, Belanger and coworkers reported a competitive [2+2] cycloaddition (Scheme 18).²⁷ They first investigated the competition between different tethered lengths. The formation of five-membered ring product **1-111** was much faster than the formation of six-membered ring product **1-134**, which was not observed in the reaction. In order to further understand the electronic impact of alkene on the [2+2] cycloaddition without the interference from steric hindrance, ketene was generated *in situ* from acid **1-135** and then reacted with two competitive styrenes with different substituents on the *para* position. The observed ratio of **1-136** and **1-137** indicated that the electron-rich alkene was favorable for the [2+2] cycloaddition. Its Hammett constant ρ was calculated to -1.39, which indicates a

modest charge development at the transition state. More important is that only *crossed* cycloadduct is obtained without any *fused* adduct.



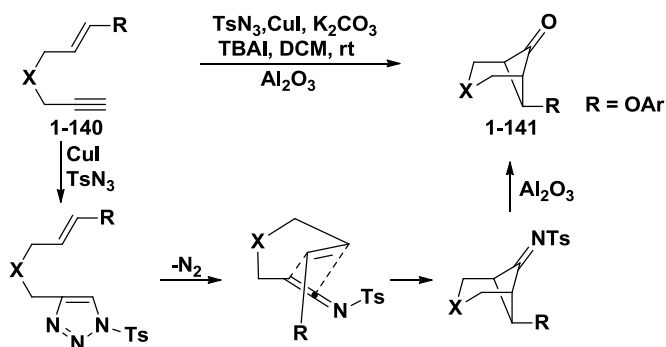
Scheme 18. Competitive [2+2] cycloadditions.

The thermal retro-ene/[2+2] cycloaddition reaction of ene-ynol ethers was reported by Minehan and coworkers (Scheme 19).⁴⁰ *tert*-Butyl alkynyl ethers **1-138** are known for their retro-ene reaction with the release of isobutylene gas at low temperature to result in the formation of ketene, which could react intramolecularly with alkene to form cyclobutanones **1-139**.



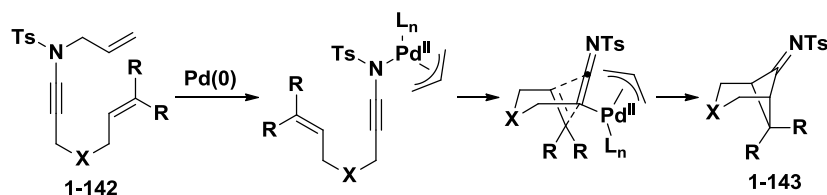
Scheme 19. The thermal retro-ene/[2+2] cycloaddition reaction of ene-ynol ether.

Recently, Tu and coworkers reported the *crossed* [2+2] cycloaddition of a ketenimine generated *in situ* from triazole under mild conditions (Scheme 20).⁴¹ 1,6-Enynes **1-140** first reacted with tosyl azide via a copper-catalyzed Huisgen cycloaddition to form triazoles, which was followed by the release of N₂ gas to afford the ketenimine intermediate. Due to the electronic partner of phenol-substituted alkene, *crossed* [2+2] cycloaddition afforded compound **1-141** after the hydrolysis.



Scheme 20. The *crossed* [2+2] cycloaddition of a ketenimine generated *in situ* from triazole.

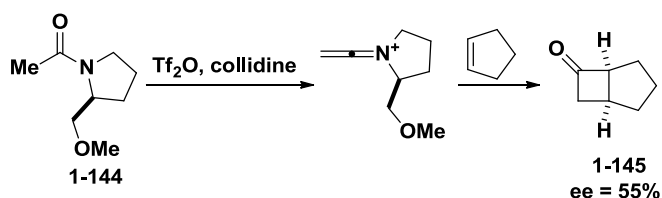
Similar work was reported by Hsung and coworkers (Scheme 21).⁴² *N*-Allyl ynamides is known to be transformed to ketenimines under the Pd catalysis. The following *crossed* [2+2] cycloadditions furnished compound **1-143**.



Scheme 21. The *crossed* [2+2] cycloadditions of ketenimines generated *in situ* from *N*-allyl ynamides.

The keteniminium ion-involved [2+2] cycloaddition was first reported by Leon Ghosez in 1972.^{43,44} An advantage of keteniminium [2+2] cycloaddition over that of ketene is that enantioselective [2+2] cycloaddition could be achieved under the assistance of chiral

amines. The first asymmetric version was reported in 1982, although only a modest enantiomeric excess (ee) was obtained (Scheme 22).⁴⁵ Its full discussion and mechanistic investigation have been reported.⁴⁶ The best result was obtained when using *trans*-2,5-dimethylpyrrolidine as the chiral auxiliary. They also proposed a molecular model to rationalize the enantioselectivity obtained (Figure 11). As described in the section 1.3.1, alkene added in-plane to the middle carbon of the keteniminium salt. The top face was blocked because of the bulky tosyl amine group. There are four possible orientations of alkene, **1**, **2**, **3**, and **4**, when attacking from bottom of the keteniminium salt. Orientations **3** and **4** are not favored due to the pseudo-axial proton in the chiral pyrrolidine ring. Orientation **2** is unfavorable, which would result from the steric hindrance between cyclopentane and tosyl amine group in the same face of cyclobutanone. High enantioselectivity was obtained through orientation **1**, and the pyrrolidine ring rotation and cyclobutane ring closure finished the synthesis of cyclobutane iminium ion. The subsequent hydrolysis afforded the enantiopure cyclobutanones.



Scheme 22. The first enantioselective [2+2] cycloaddition.

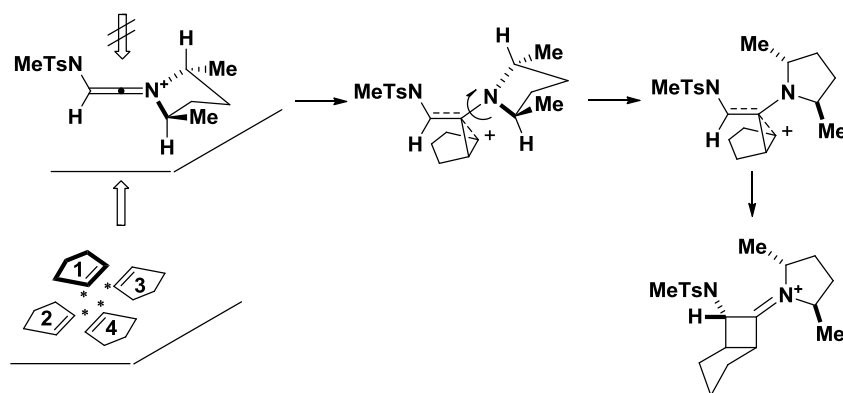
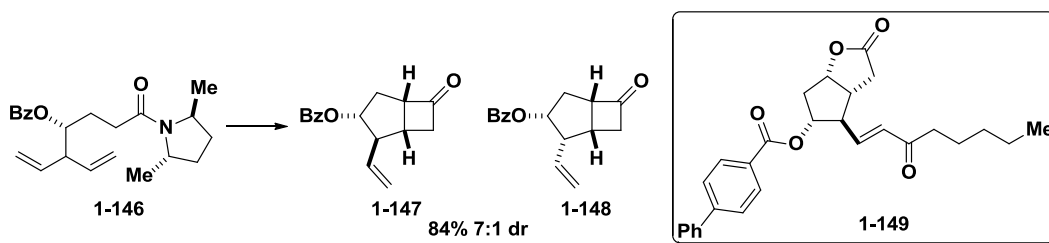


Figure 11. Stereochemistry of keteniminium-ion-involved [2+2] cycloaddition.

The first intramolecular keteniminium ion-involved asymmetric [2+2] cycloaddition was reported in 1990.⁴⁷ Since then, this asymmetric version has been utilized to synthesize the advanced intermediate of prostaglandins (Scheme 23).^{48,26}



Scheme 23. Key step for the synthesis of an advanced intermediate of prostaglandin.

1.3.3 Results and discussions

The preparation of [2+2] cycloaddition starting materials. Although our eventual goal was to achieve an asymmetric [2+2] cycloaddition, we first tested the strategy using the racemic [2+2] adduct. Based on that work, we should be able to transfer the established conditions to the asymmetric cycloaddition. As described before, the racemic [2+2] product could be obtained through either a ketene or keteniminium ion (Figure 12). Ketene is usually generated from acyl chloride under basic conditions and high temperature, and the following

cyclization directly affords cyclobutanone. Alternatively, the amide can form a keteniminium ion under strong dehydration conditions such as triflic anhydride, and the following cycloaddition affords [2+2] iminium ion, which is followed by hydrolysis to give cyclobutanone. There are two more steps to get cyclobutanones through the keteniminium ion, amide formation and hydrolysis of keteniminium ion. Despite that, this method offers the significant advantage that enantiopure cyclobutanone could be obtained from this if the pyrrolidine portion is replaced by a chiral auxiliary, such as *trans*-2,5-dimethylpyrrolidine (2*R*,5*R* or 2*S*,5*S*). Therefore, we opted to explore both methods to synthesize the racemic cyclobutanones. While the ketene synthetic route gives the cyclobutanone quickly, the keteniminium ion synthetic route establishes the methods possible to the asymmetric [2+2] cycloaddition.

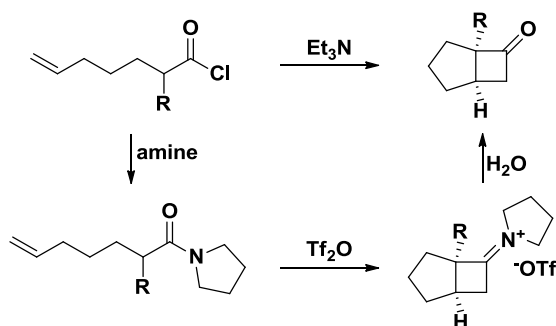
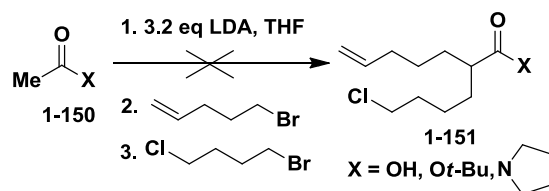


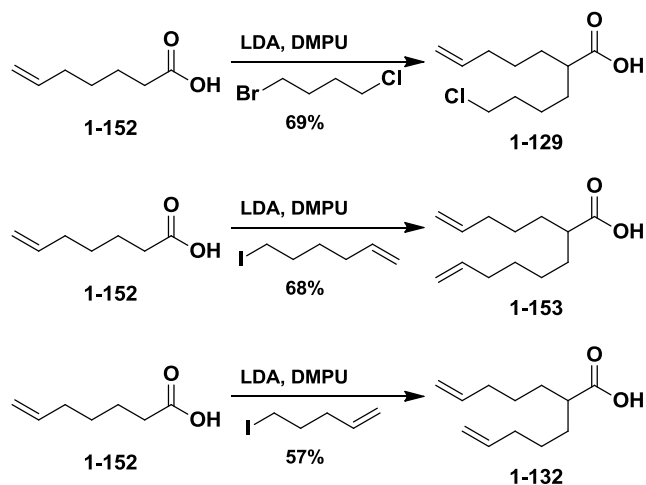
Figure 12. General scheme of [2+2] cycloaddition.

Dowd and co-workers reported the one-pot dialkylation of the dianion of acetic acid using 3.2 eq LDA to prepare compound **1-151** (X = OH) (Scheme 24).³⁸ Unfortunately, this direct route was unsuccessful in our hands. We also tried to use *tert*-butyl acetate and amide **1-155** as substrates; however, they were still not successful.



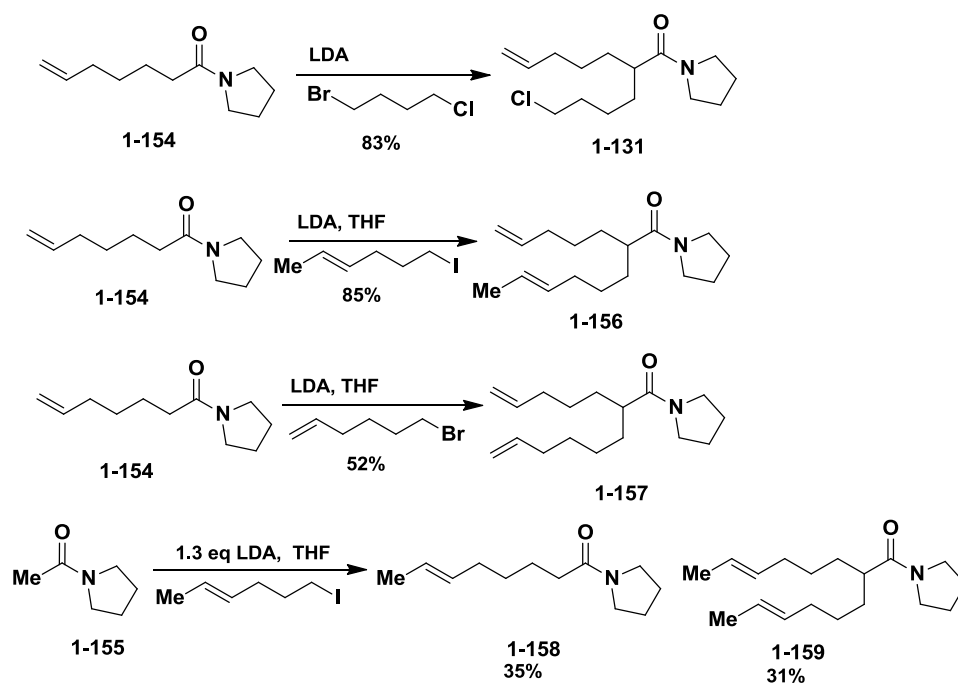
Scheme 24. Unsuccessful attempts of one-pot dialkylation.

Thus we turned our attention to the preparation of the [2+2] starting materials through mono-alkylation. Commercially available hept-6-enoic acid **1-152** was transformed to acid **1-129**, **1-153**, and **1-132** respectively in modest yields using LDA as base and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) as the additive (Scheme 25).



Scheme 25. Synthesis of [2+2] cycloaddition starting materials (acids).

The corresponding amides were also prepared by the simple alkylation of amide **1-154** with the corresponding halide partners (Scheme 26). Amide **1-159** was the over-alkylated product of amide **1-155** with (*E*)-6-iodo-2-hexene, obtained in 31% yield.

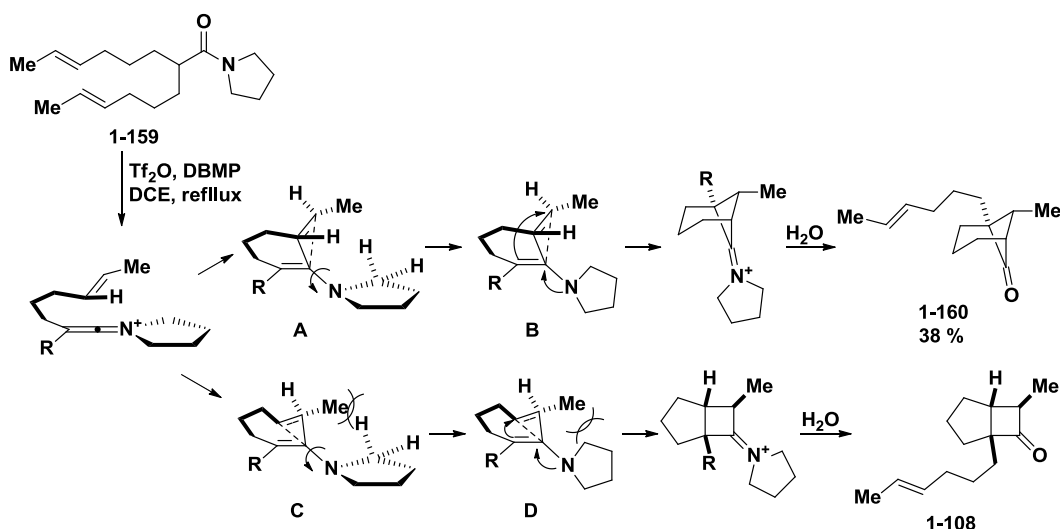


Scheme 26. Synthesis of [2+2] cycloaddition starting materials (amide).

[2+2] cycloaddition reaction. Based on our retro-analysis in Figure 5, we first focused on the preparation of cyclobutanone **1-108** from amide **1-159** under keteniminium ion-mediated [2+2] cycloaddition conditions (Scheme 27). However, we did not get our desired product. Instead, compound **1-160** was obtained in 38% yield. We speculated that methyl substituted alkene is favored for *crossed* [2+2] cycloaddition. As known, ^1H and ^{13}C chemical shifts in the NMR spectroscopy can indicate the electron density of atoms. For amide **1-159**, both H_1 and H_2 have the same chemical shift, and the ^{13}C chemical shift of C_2 is 131.1, whereas C_1 is 125.0 (Figure 13). While this is consistent with the view that carbon C_1 is slightly more nucleophilic than C_2 , the electronic contribution was insufficient to overcome the steric hindrance of the [2+2] cycloaddition leading to bridged product.

There are two possible pathways in the [2+2] cycloaddition, which lead to **1-160** and **1-108**, respectively. Both pathways use the π electrons of the alkene as the nucleophile. But, the actual bond formation occurs on the different carbons of alkene. Because both carbons of

alkene have similar nucleophilic ability, steric hindrance plays more importance in this reaction. In intermediate **C**, the bond was formed between the terminal carbon of alkene and middle carbon of keteniminium ion, so the methyl group is close to the pseudo-axial hydrogen of the horizontal pyrrolidine, causing the steric hindrance. When the pyrrolidine orientation was rotated to the perpendicular plane, even more steric hindrance resulted between the methyl group and two hydrogens of the pyrrolidine in transition state **D**. However, when the bond was formed between the internal carbon of alkene and middle keteniminium ion, the methyl group is far from the two hydrogens of pyrrolidine ring. This is the reason why cyclobutanone **1-160** is the sole product.



Scheme 27. Crossed [2+2] cycloaddition of methyl-substituted amide **1-159**.

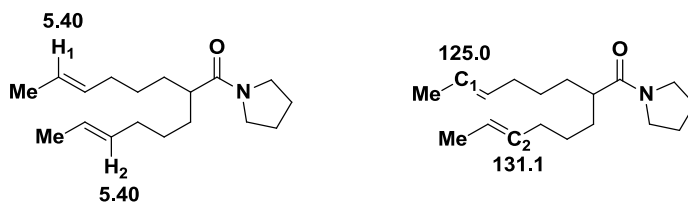
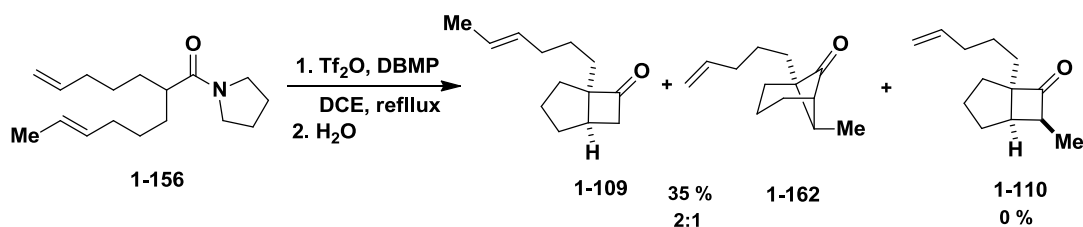


Figure 13. ^1H and ^{13}C chemical shifts of amide **1-159**.

When we treated amide **1-156** with [2+2] cycloaddition conditions, cyclobutanone **1-109** and **1-162** were obtained in 35% yield with 2:1 ratio. We did not observe any production of **1-110**. It meant that there is only minor energy difference between pathways leading to methyl-substituted olefin and non-methylated olefin. As discussed in Figure 13, reaction occurs on carbon C₄ due to steric hindrance although there is not too much difference between the nucleophilicity of C₃ and C₄ (Figure 14). Carbon C₁ is more nucleophilic than C₂ from both points. Although NMR is not a good predictor of this reaction, the product ratio indicates that the difference is pretty small. Furthermore, both compounds are inseparable.



Scheme 28. [2+2] cycloaddition of amide **1-156**.

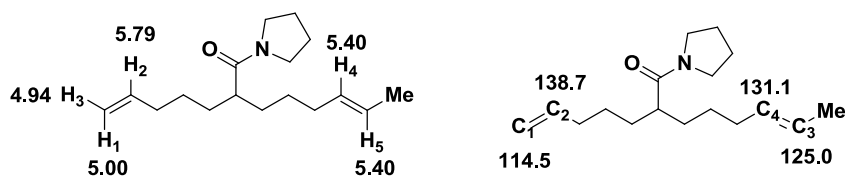
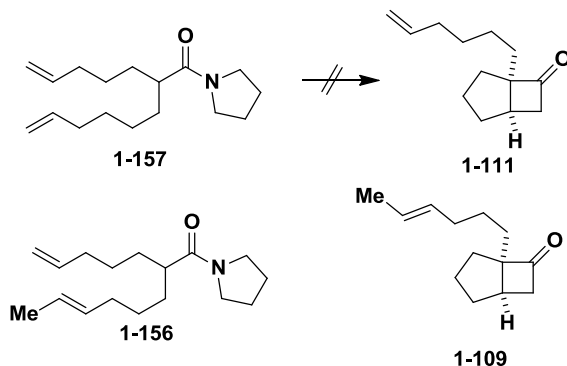


Figure 14. ¹H and ¹³C chemical shifts of amide **1-156**.

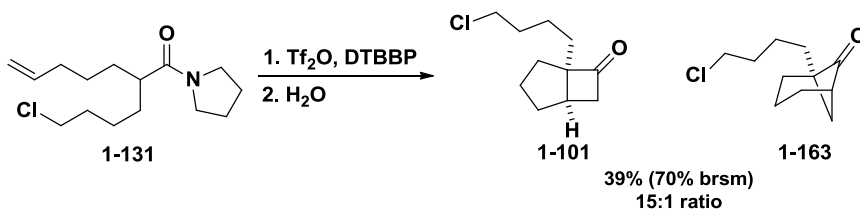
Building on the lessons learned from our first two attempts, we turned our attention to prepare non-methylated cyclobutanone precursors. Amide **1-157** was treated under the [2+2] cycloaddition conditions, a mixture of [2+2] cycloadducts were obtained, along with the double-bond migrated amide **1-156**. Specifically, we identified cyclobutanones **1-111** and **1-109** in the reaction mixture. The reaction conditions provided several opportunities for double bond migration: 1) at starting material stage; 2) at keteniminium ion stage, 3) at

iminium ion stage. We have not established at which stage the migration of double bond occurs.



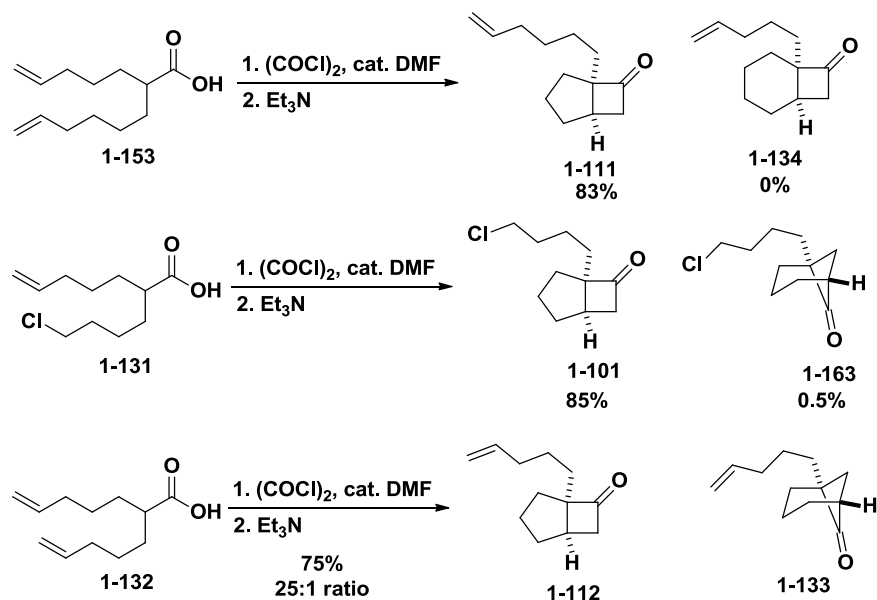
Scheme 29. [2+2] cycloaddition of amide **1-157**.

Cyclobutanone **1-101** was also prepared by keteniminium ion-mediated [2+2] cycloaddition from **1-131** in 39% yield as a mixture with **1-163** with 15:1 ratio (Scheme 30). Both compounds are inseparable.



Scheme 30. [2+2] cycloaddition of amide **1-131**.

In comparison, ketene-mediated [2+2] cycloadditions were also tested to get the same compounds, with better results (Scheme 31). As reported,²⁷ the cycloaddition of **1-153** did not produce any of **1-134**.



Scheme 31. Ketene-mediated [2+2] cycloadditions.

Spectral difference of *crossed* and *fused* [2+2] cycloadducts. Both ketene and keteniminium ion mediated [2+2] cycloadditions produced *fused* and *crossed* [2+2] cycloadducts. From spectral data, we can clearly differentiate them (Figure 15). Although both compounds have one carbonyl carbon, one quaternary carbon, and one tertiary carbon, the proton connecting to the tertiary carbon is also at the α -position of carbonyl group for cyclobutanone **1-163**. Its ^1H and ^{13}C chemical shifts are markedly different from those of *fused* cyclobutanone **1-101**.

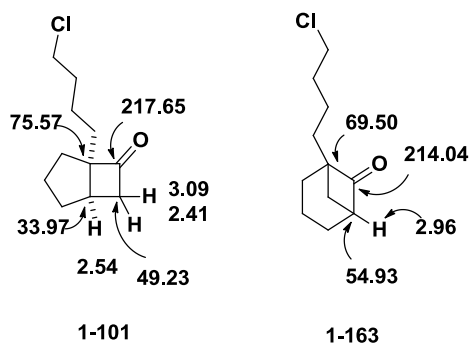
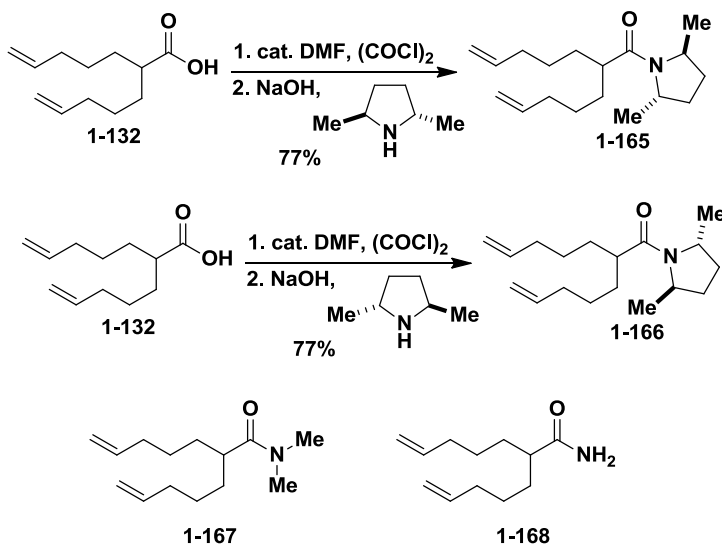


Figure 15. Spectral data of *fused* and *crossed* [2+2] adducts.

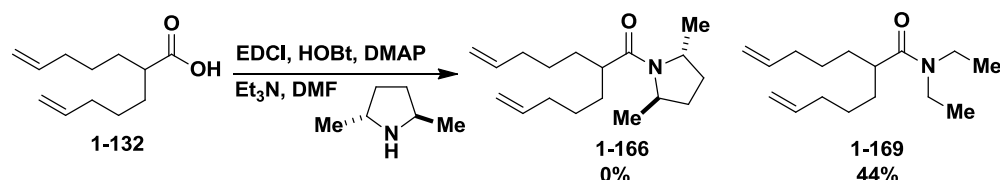
Preparation of chiral amide. As our research progressed, we also needed to access enantiopure cyclobutanone **1-108**. Based on the reported intramolecular asymmetric [2+2] cycloaddition,²⁶ the desired chiral auxiliary is (2*R*,5*R*)-(-)-*trans*-2,5-dimethylpyrrolidine. Because it is pretty expensive (\$190/50 mg, Aldrich), we first tried to optimize the reaction conditions using its enantiomer, (2*S*,5*S*)-(+)-*trans*-2,5-dimethylpyrrolidine (N-Boc, \$188/500 mg, Aldrich).

First, acid **1-132** was converted to acyl chloride using oxalyl chloride under the catalysis of DMF and condensed with (2*S*,5*S*)-(+)-*trans*-2,5-dimethylpyrrolidine to afford amide **1-165** using aqueous NaOH as the base (Scheme 32). The corresponding **1-166** was also prepared by this method. In some reactions, dimethyl amide **1-167** was obtained as a byproduct. This likely resulted from the decomposition of Vilsmeier reagent generated from DMF and oxalyl chloride to eject dimethyl amine. Amide **1-168** is also observed as a byproduct when the reaction was quenched with saturated aqueous ammonium chloride.



Scheme 32. Synthesis of chiral amides.

During the course of reaction optimization, we were surprised to find that amide **1-169** was obtained as the major product when triethylamine was used as the base (Scheme 33).



Scheme 33. Preparation of chiral amide using triethylamine as base.

When we tried to rationalize this result, a retro-ene reaction is a good explanation although there is another possibility (**A**) there (Figure 16). Ketene, generated from acyl active anhydride under basic conditions, would react with triethylamine to form a zwitterion. One possibility is that the nucleophile in the reaction might attack the α carbon in the amine to form the product (pathway **A**). Under the assistance of the enolate intermediate, a retro-ene reaction may proceed to form the amide product, along with the release of ethylene as a byproduct (pathway **B**). Another possibility is that ene reaction occurred in an intermolecular way without the support from an enolate intermediate (pathway **C**).

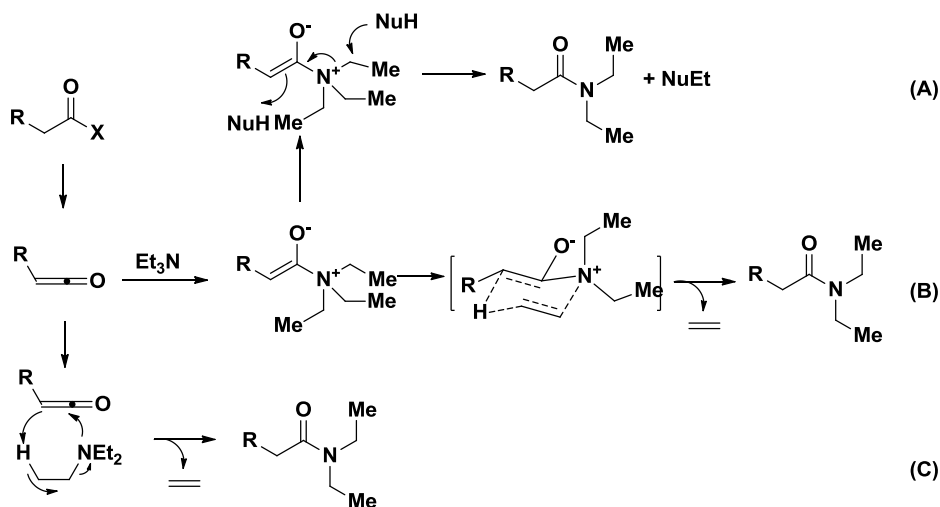
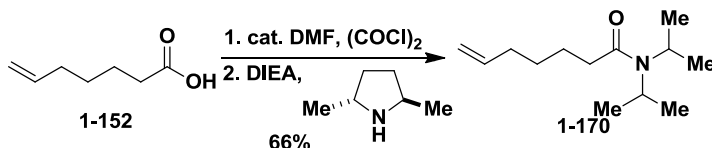


Figure 16. Retro-ene reaction.

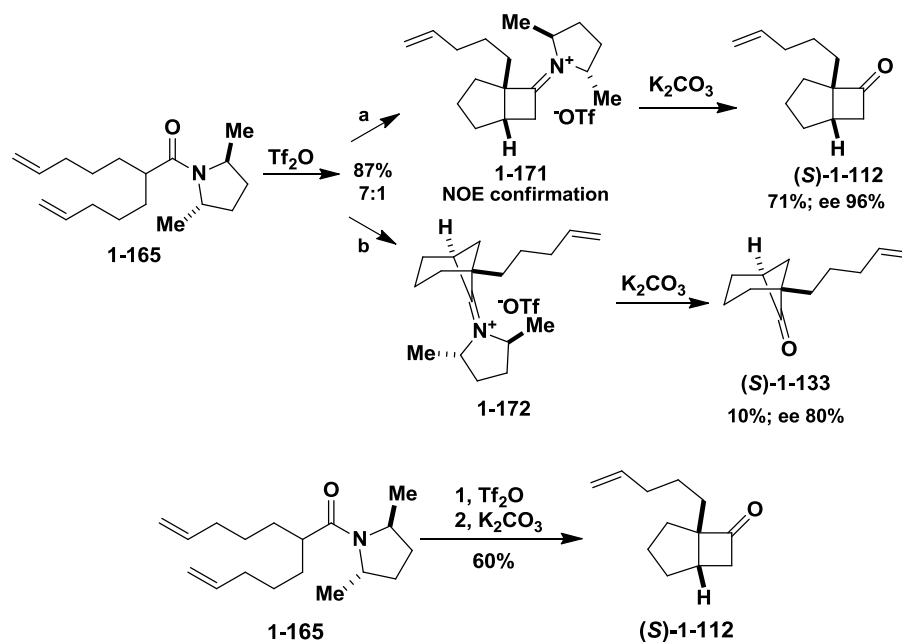
In order to differentiate them, DIEA was used as the base in the reaction (Scheme 34) since the nucleophilicity of DIEA is much weaker due to the steric hindrance of the bulky

isopropyl group. The formation of diisopropyl amide **1-170** would indicate that the ene reaction pathway is the likely explanation.



Scheme 34. Diisopropylamide formation.

Asymmetric [2+2] cycloaddition. With chiral amide in hand, this material was subjected to the [2+2] cycloaddition conditions²⁶ to afford a mixture of iminium ions **1-171** and **1-172** (Scheme 35). Fortunately, we found that these products are stable to silica gel column isolation, and we are able to confirm the relative stereochemistry of **1-171** by NOE experiments (Figure 17). Hydrolysis attempts in neutral water, which usually worked for hydrolysis of pyrrolidine substrate, did not work for this chiral bulky iminium substrate. Successful hydrolysis was obtained under basic conditions to afford cyclobutanones (**S**)-**1-112** and (**S**)-**1-133** with 96% ee and 80% ee, respectively, which is determined by GC. Both steps can be done in a one-pot sequence, analogous to racemic substrates.



Scheme 35. Synthesis of enantiopure cyclobutanone.

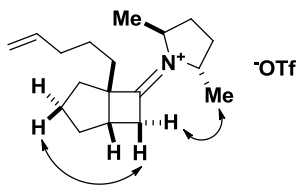
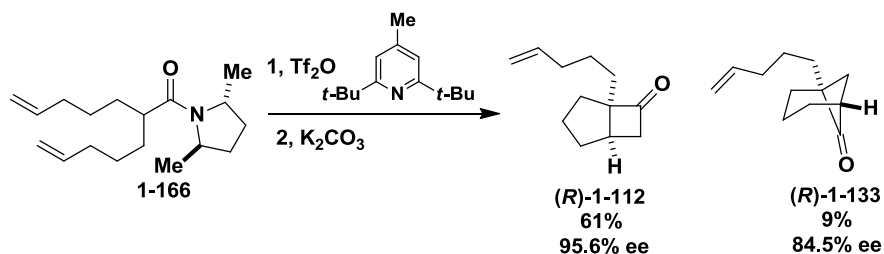


Figure 17. NOE correlations for iminium ion **1-171**.

The same result was obtained when (2*R*,5*R*)-(-)-*trans*-2,5-dimethylpyrrolidine was used as the chiral auxiliary (Scheme 36). GC chromatograms of cyclobutanones **1-112**, (*R*)-**1-112** and (*R*)-**1-133** were shown in Figure 18, Figure 19, and Figure 20.



Scheme 36. Synthesis of cyclobutanone (*R*)-**1-112**.

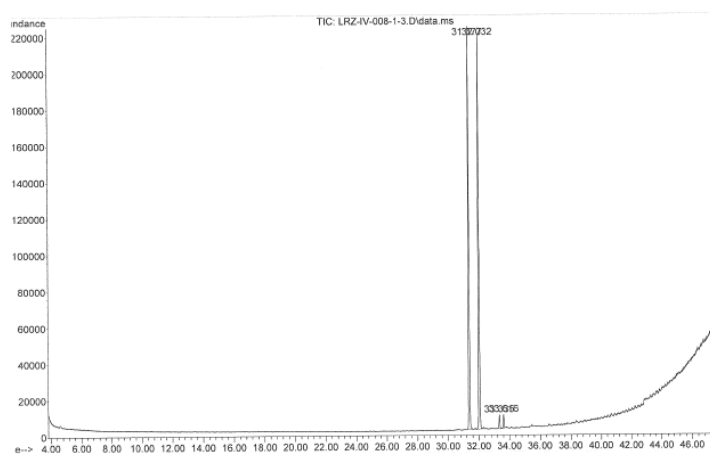


Figure 18. GC chromatogram of **1-112**.

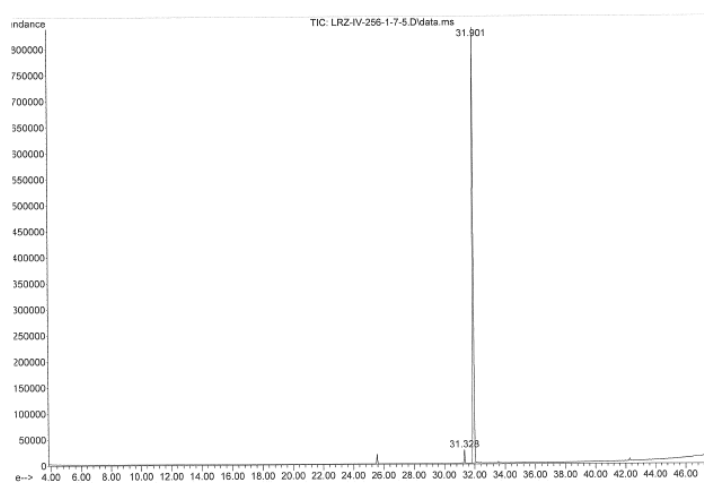


Figure 19. GC chromatogram of **(R)-1-112**.

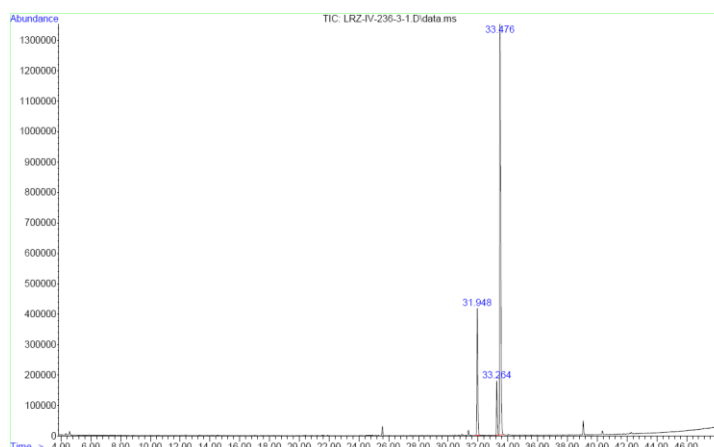


Figure 20. GC chromatogram of **(R)-1-133**.

Asymmetric [2+2] cycloaddition model. The C_2 -symmetry of the keteniminium ion allows a thorough discussion of the stereochemical outcomes using only one side chain (Figure 21). Theoretically, there are eight attack directions of olefin to keteniminium ion. The side chain under consideration approaches from the top of keteniminium/pyrrolidine plane, and therefore the olefin in the side chain cannot reach the keteniminium ion from the bottom of keteniminium/pyrrolidine plane because there are only three carbons between olefin and the end carbon of keteniminium ion. So attack directions **d**, **e**, and **f** are impossible for this scenario. There are two bulky methyl groups on the two sides of keteniminium ion in the keteniminium/pyrrolidine plane, and these can block the olefin's attack to the keteniminium from perpendicular to the perspective of the keteniminium/pyrrolidine plane. Moreover, these kinds of attacks (**c** and **g**) are not favorable based on the computational results. Direction **h**'s attack is also blocked by the up methyl group. The favored attack directions should lie in the direction **a** or **b**, or between **a** and **b**.

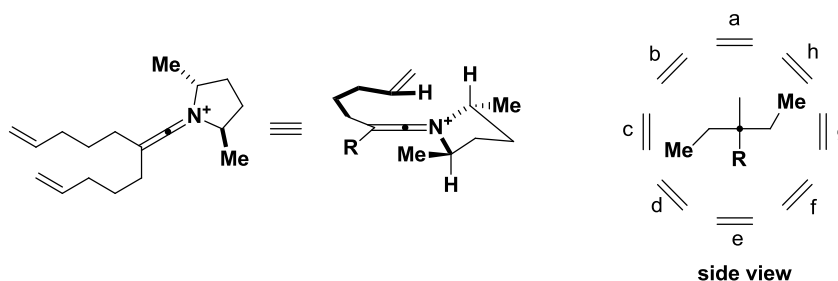


Figure 21. Attack directions of olefin to keteniminium ion.

Besides the attack directions of olefin, the olefin orientation also affects the stereochemical outcome of this reaction (Figure 22). There are two orientations of olefin: **A** and **B**. One's sidechain is outward (**A**), and the other's inward (**B**). Each one has two interaction models depending on which carbon of double bond contributes more to this interaction. The nucleophilic internal carbon of intermediate **A** attacks the middle carbon of keteniminium ion to form intermediate **C**. Although it is the π electrons of the double bond which act as the nucleophile during the attack, the bond formed between keteniminium middle carbon and internal olefin carbon is actually short in order to generate *crossed* [2+2] product. Along with that, a primary unstable carbocation is also formed. The following rotation of pyrrolidine ring provides a chance of electron flow from lone pairs of nitrogen to enamine bond, and finally they go to the primary carbocation carbon to form bridged bicycle adduct **K**. The pathway A-D-H-L is similar except the short bond forms between terminal olefin and middle keteniminium carbon, and the carbocation is a more stable secondary one. This pathway would afford the fused cyclobutane derivative **L**. There is one more argument that a relatively strained cyclohexene is formed in the pathway A-C-G-K instead of a relatively loose cycloheptene for pathway A-D-H-L, which would rationalize why the fused [2+2] cycloadduct is the major one. The pathways B-E-I-M and B-F-J-N afford the corresponding enantiomers by the same logic as above.

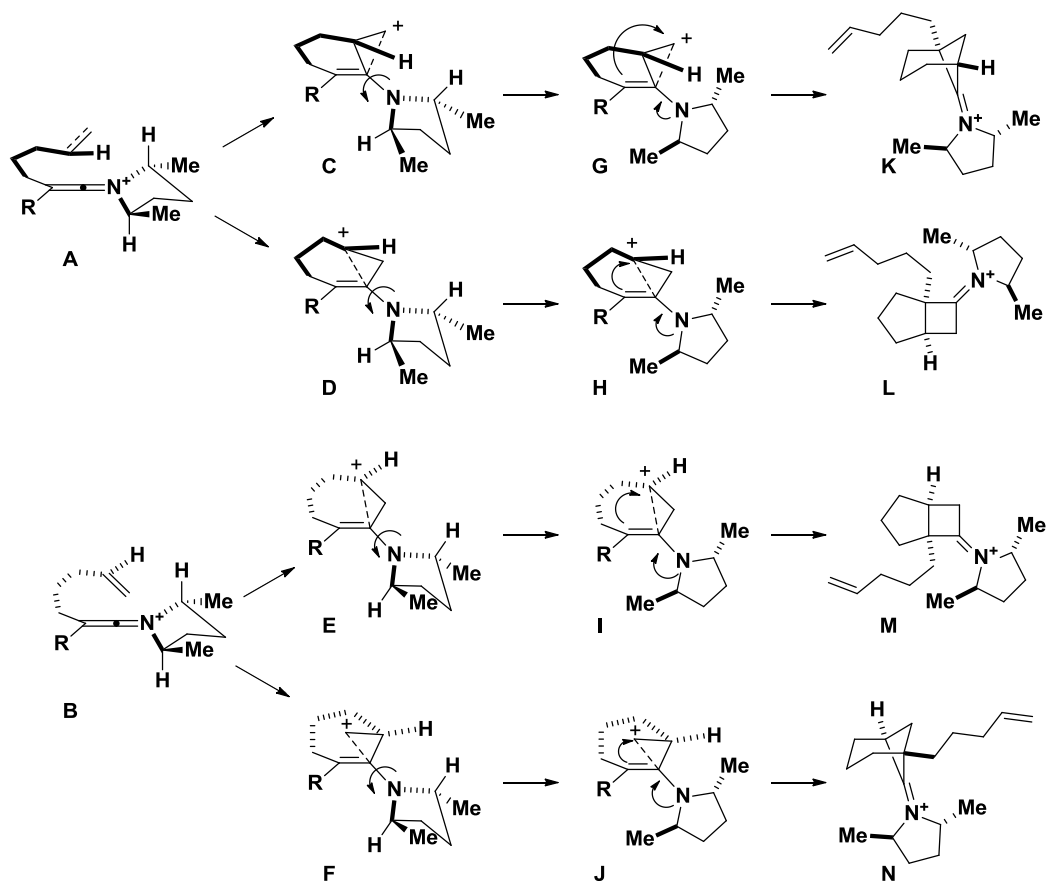


Figure 22. *Fused and crossed asymmetric [2+2] cycloaddition pathways.*

In order to clarify the relative energy diagram, different views for each intermediate are shown in Figure 23. The bonded carbon of alkene in each intermediate is always closer to the middle carbon of keteniminium ion while the un-bonded carbon of alkene is much closer to the terminal carbon of keteniminium ion. As discussed above, the ring strain and carbocation stability make **D** more stable than **C**. The attack direction of the double bond makes the conformation of intermediates **E** and **F** more strained, clearly indicated by their side views. This explained the origin of high enantioselectivity. From top view of **F**, the existence of up methyl group (at pseudo equatorial position) affords a primary carbocation closer to terminal carbon of keteniminium ion, and facilitates the second bond-formation. A similar situation is seen for intermediate **D**. The pseudo axial hydrogen atom does not have

much impact on the conformations of these intermediates because its small size does not allow steric interaction with the double bond or even its attached hydrogens. Compared to the energy difference between **C** and **D**, the difference between **E** and **F** is much less. In other words, the energy difference of **D** and **E**, which leads to the generation of (*R*)-**1-112** and (*S*)-**1-112**, is higher than that of **C** and **F**, leading to the formation of (*R*)-**1-133** and (*S*)-**1-133**. This is the reason why the enantiomeric excess of *crossed* product is less than *fused* [2+2] product.

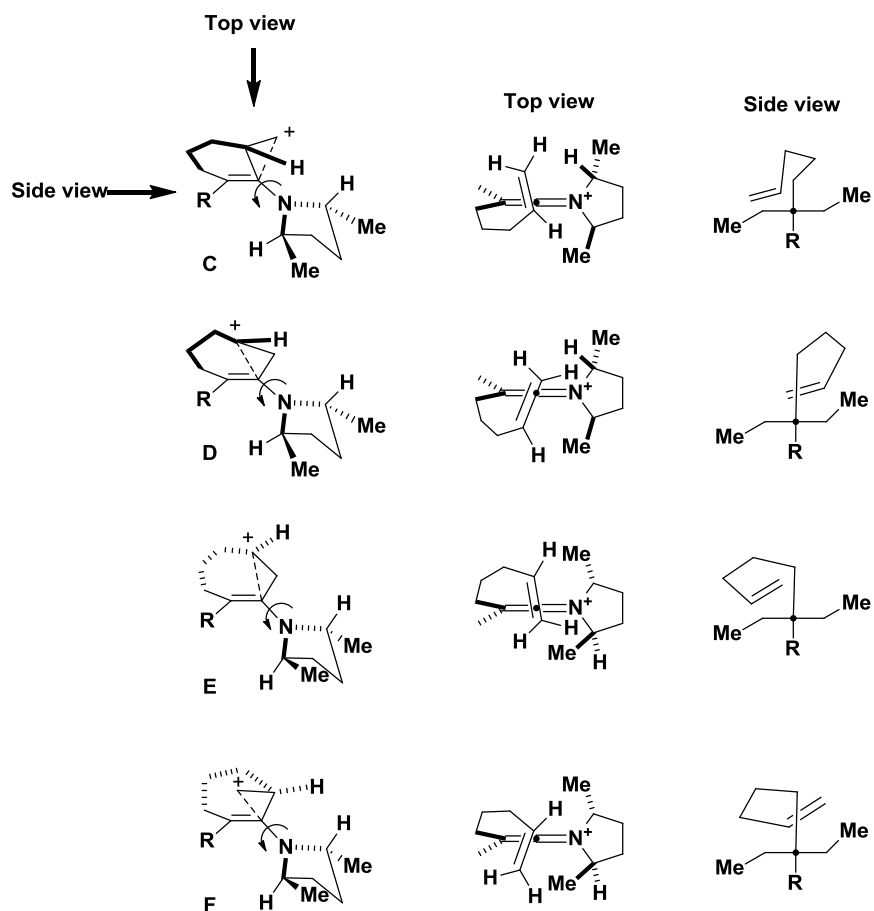
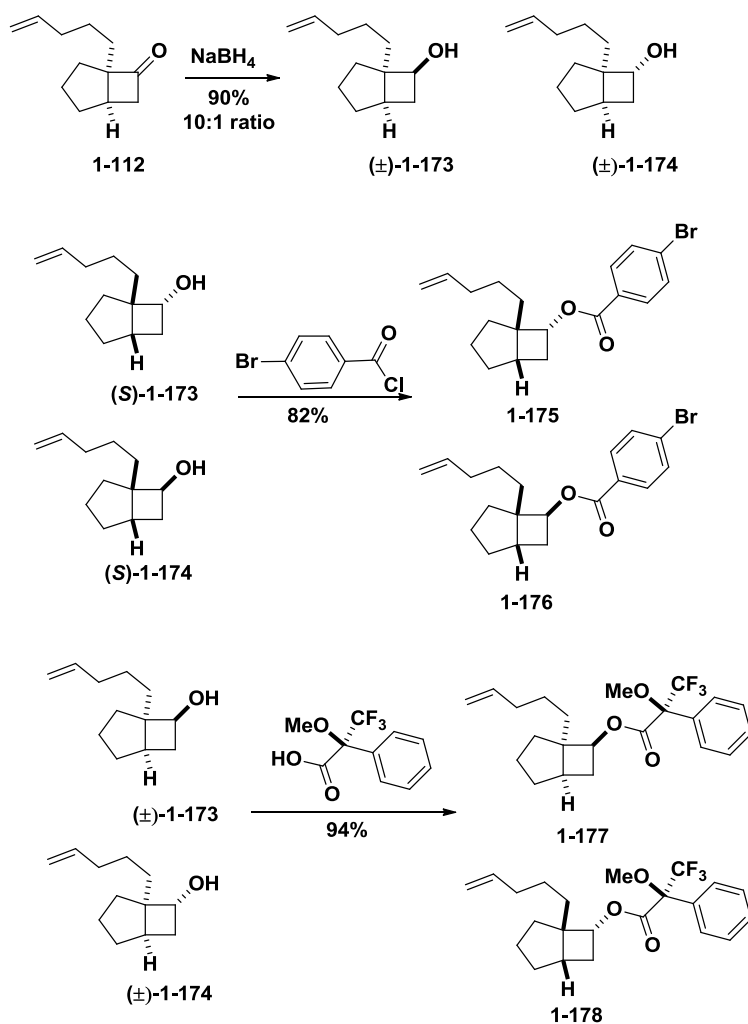


Figure 23. Different views of intermediates in the asymmetric [2+2] cycloaddition.

Absolute configuration determination. Although comparison to known examples allowed us to deduce the absolute configuration of our products, we still desired to further

confirm our assignment. The most straightforward way to determine absolute configuration is through heavy-atom assisted crystallography, if possible. We first reduced the ketone to alcohol (10:1 ratio), then condensed with 4-bromobenzoyl chloride to form ester **1-175**. However, recrystallization attempts did not give crystalline material, but rather a fine powder. Similar crystallinity issues arose using Mosher's esters **1-177** and **1-178**. An alternate approach to determine its absolute configuration would be measuring the chemical shift difference between **1-177** and **1-178**; however, these esters were inseparable. Due to the existing difficulty, we tried to determine it later by the modification of tricyclic lactam scaffold.



Scheme 37. Studies toward absolute configuration determination.

1.4 Electrochemistry-mediated synthesis towards pinnaic acid

1.4.1 Introduction

In recent years, there has been a considerable increase in the use of electrochemical reactions in organic synthesis although it is far from a routine technique. A tutorial review⁴⁹ and several comprehensive reviews^{50,51,52,53,54} have summarized recent advances in this field.

A powerful tool in organic chemistry, electrochemistry can selectively introduce and remove electrons from organic molecules under mild conditions to generate a wide variety of reactive intermediates (radical-ions) on any scale. Many of these transformations are unique to electrochemistry. However, the requirement of specialized equipment puts off many synthetic chemists.

There are two types of organic electrochemical reactions, oxidations and reductions (Figure 24). Oxidations take place at the anode, and one/two electrons are removed from electroactive species to generate highly reactive intermediate radical-cations, commonly referred to as anodic oxidation. Likewise, one or two electrons are added to electroactive species at the cathode to produce highly reactive intermediate radical-anion, named as cathodic reduction. A variety of cyclization reactions can ensue from the initial radical-ion species, named as anodic cyclization and cathodic cyclization.

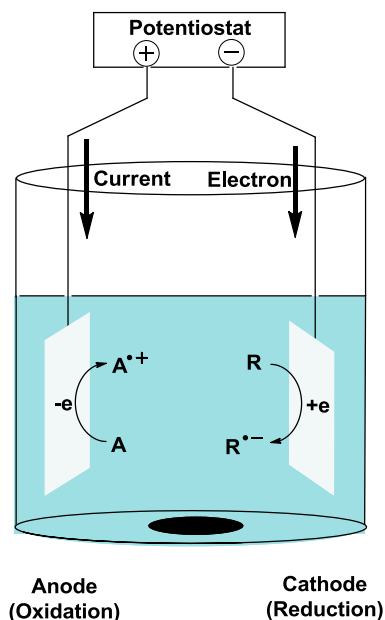


Figure 24. Schematic of an electrochemical setup.

Apparatus. Electrochemical setups usually contain an electroactive species, solvent, electrolyte, at least two electrodes (anode and cathode, or reference electrode), and/or various additives. In Table 1, there are commonly used components for each category. The choice of solvents is fairly broad, and electrolytes are typically salts that dissociate into ions and make the solution conductive. Electrodes have to be stable to the reactions conditions, and allow for the transfer of electrons in solution. The electrode's physical form can provide a way to moderate the current density on the surface area of electrode to accomplish the current-density-sensitive reactions. In order to achieve the best result of any chemical reactions, the choice of aforementioned components often need to be optimized.

Table 1. Common components in the organic electrochemistry.

Solvent	Methanol, THF, acetic acid, dichloromethane, acetonitrile, nitromethane, water.
Electrolyte	Lithium perchlorate (LiClO_4), tetrabutylammonium tetrafluoroborate (Bu_4NBF_4), tetraethylammonium tosylate (Et_4NOTs), tetrabutylammonium acetate (Bu_4NOAc), any other tetralkylammonium salt (R_4N^+).
Anode material	C (graphite), Pt, Au, Pt-Ti, TiO_2 -Ti, RuO_2 -Ti, PbO_2 -Pb, RVC (reticulated vitreous carbon).
Cathode material	C (graphite), almost any metal.
Electrode's form	Rod, plate, wire, net gauze, sponge (RVC).

Besides the above parameters, an electron source must be used to apply a potential, usually achieved by a potentiostat. It can also be used to control the current during the constant current experiments.

There are two types of electrochemistry experiments: constant current and controlled potential. In a constant current experiment that the flow of the current through the cell is held at a constant value by the potentiostat, the potential at the electrode surface begins to rise due to the resistance of electrolyte. And it will continue to rise until the oxidation potential of electroactive species is reached. Once reached, it will keep unchanged for the time period that all the material at this oxidation potential is consumed. After that, the potential will continue to climb until the oxidation potential of a second electroactive species or the solvent is reached. A disadvantage of this experiment is over-oxidation when the substrate has more than one electroactive functional group.

Selective oxidation can be achieved in controlled potential experiments by keeping the potential at a set value. As the electroactive species is consumed, the resistance increases and then the current decreases, and hence it takes longer to oxidize or reduce the starting material. The disadvantage is that it may be difficult to drive a controlled potential experiment to completion.

There are two basic choices for the construction of electrochemical reactors: an undivided cell or a divided cell. In the undivided cell set-up, both reduction and oxidation are allowed to happen within the same compartment, which could be a beaker, vial, or round-bottom flask. More attention needs to be given to the chemistry occurring at the auxiliary electrode because the substrate there is exposed to all species present in the reaction, such as starting material, newly-formed product, and electrolyte. Byproducts generated there might affect the starting materials or products. Typically, undivided cells are commonly used for constant current experiments because of their ease of construction.

The divided cell is an alternative solution for this cross-interference but more complex. It uses a small, porous frit to physically separate the anodic and cathodic

compartments, which only allows for the transfer of electrons. It can be employed in either constant current or controlled potential experiments.

Anodic oxidation. Anodic oxidation takes one/two electrons away from a neutral substrate to generate a reactive radical cation intermediate that can undergo either direct manipulations or cascade reactions. This offers synthetic chemists a unique opportunity to construct new bonds while the functionality is either increased or preserved in order to further manipulate the generated product.

Two common applications of this chemistry are amidic oxidation and olefin coupling. Amidic oxidation is the oxidative generation of *N*-acyliminium ions from amides and carbamates (Figure 25). One of the lone pair of electrons in the nitrogen atom of amide is removed to produce nitrogen radical cation. The hydrogen in the neighboring carbon of nitrogen atom is removed as a proton while one additional electron is also lost to generate an *N*-acyliminium ion, which is followed by the nucleophilic attack to produce the product.

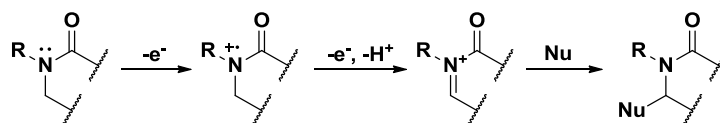


Figure 25. The mechanism of amidic oxidation.

Intramolecular anodic olefin coupling reactions take one electron away from an electron-rich alkene (Figure 26). The generated radical cation may be trapped with an intramolecular nucleophile to form a new C-C bond along with the proton loss from the nucleophile. The newly-formed radical usually reacts with protic solvent to form the product. These reactions reverse the polarity of the electron rich alkene to be oxidized, and transform it into an electrophile. Overall, the oxidation of a substrate having two nucleophiles leads to a coupling of the two nucleophiles. Such transformations open up the possibility of developing new methods for the construction of ring systems.

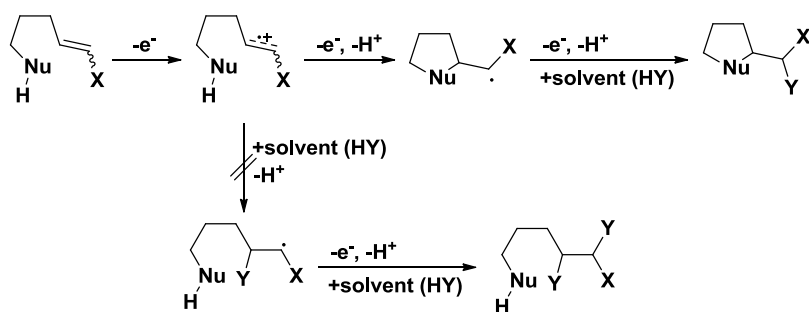
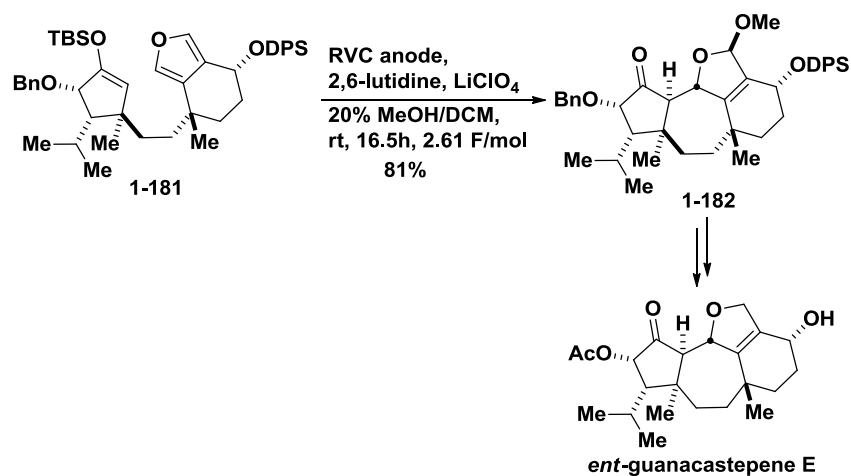


Figure 26. The mechanism of olefin coupling.

There are some questions as to why the generated radical cation from electron-rich alkene does not react with protic solvent to form new products (Figure 26). Intramolecular reaction is one of the arguments. But there are some specific explanations from an electrochemistry standpoint. It is generally accepted that the oxidation/reduction of the electroactive species takes place on the electrode surface in the compact layer (a few Å away from electrode). Far from the anode, the potential drops exponentially through the bulk solution, where the potential is not high enough to oxidize the electroactive species. For olefin coupling, the cyclization with inactive nucleophile is kinetically faster than the diffusion through bulk solution. This is the reason that highly reactive radical-cations and radical-anions can be generated in the presence of nucleophilic and protic solvents.

Amidic oxidation and olefin coupling reactions have been utilized in the syntheses of complex molecules. There is a wonderful demonstration of intramolecular anodic olefin coupling reaction's application in the total synthesis of natural product *ent*-guanacastepene E (Scheme 38).^{55,56} Trauner and coworkers successfully achieved the construction of guanacastepne polycyclic skeleton using furan as the electron-rich alkene and TBS enol ether as the nucleophile to construct **1-182** in this olefin-coupling reaction.



Scheme 38. Application of olefin coupling in the total synthesis of guanacastepene E.

Cathodic reduction. In comparison to the popularity of anodic oxidation, cathodic reduction is less used in organic reactions. But it has its own unique characteristics. As opposite to anodic oxidation, cathodic reduction adds one/two electrons to electroactive species (Figure 27). So it can reverse the polarity of its substrate, such as a carbonyl group, electron-deficient alkene, and the β carbon of α , β -unsaturated carbonyl compound, and then make the reactive carbon become nucleophilic instead of its electrophilic character.⁵⁷

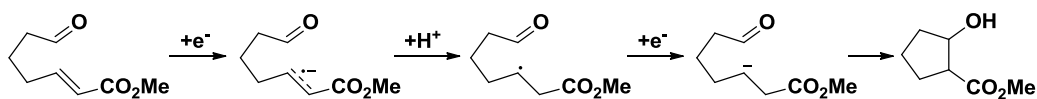
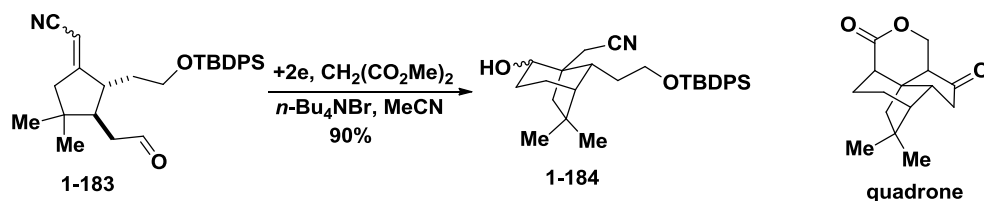


Figure 27. A cyclization involving cathodic reduction.

One demonstration is the formal synthesis of the natural product quadrone (Scheme 39).⁵⁸ Cathodic reduction was utilized in the key step to build the bicyclic ring **1-184** by Little and coworkers.



Scheme 39. Application of cathodic reduction in the formal synthesis of quadrone.

In conclusion, electrochemistry is a the powerful tool in organic chemistry and it is beginning to gain more popularity due to its unique characteristics. Its prominent character is to trigger *umpolung* reactivity for multiple functional groups.

1.4.2 Electrochemistry apparatus

Specialized equipment, especially the potentiostat, can be viewed as an obstacle by synthetic chemists to utilize electrochemical methodology as a traditional technique. Moeller and coworkers successively found that 6-volt lantern batteries could be used to get electrochemical results similar to those using commercial equipment.⁵⁹ Recently, Boydston and coworkers demonstrated the organocatalyzed anodic oxidation of aldehydes to esters powered by D-cell batteries.⁶⁰

In order to expand the utility of the intramolecular Schmidt reaction in organic synthesis, we were interested in developing a method to modify such Schmidt products (Figure 28). There are also a number of potential applications toward to the total syntheses of natural products, such as tuberostemonine.

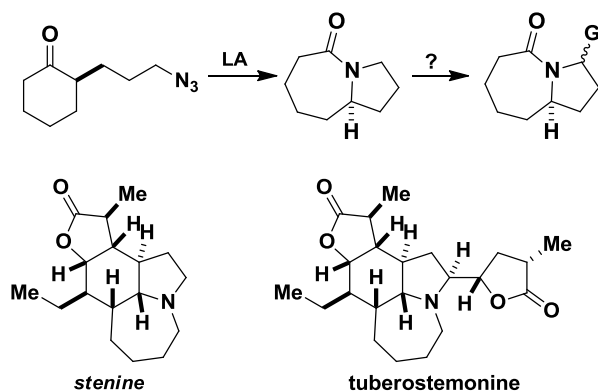


Figure 28. Diversification of a representative Schmidt product.

Dr. Kevin Frankowski of our lab conceived of the use of a discarded recharging adapter of electronic devices, such as mobile phones, as a suitable voltage power source for electrochemical reactions. He successfully obtained positive results for amidic oxidation to generate the acyliminium ion precursors (Figure 29).⁶¹

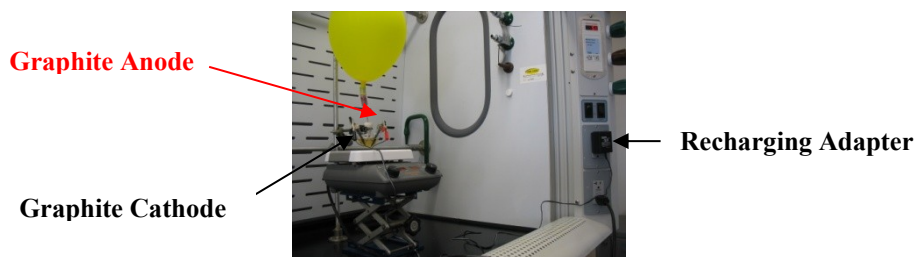
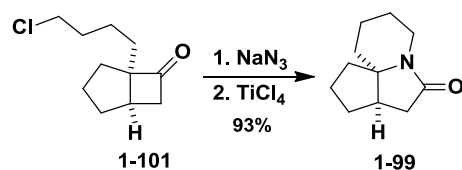


Figure 29. Home-made electrochemistry apparatus.

The adapter Kevin used is 6V/300mA, and the adapter I used is 5.0V/0.7A. Each afforded good results. The current shown on the device's label is the maximum current, but the voltage is the actual potential applied to our reaction.

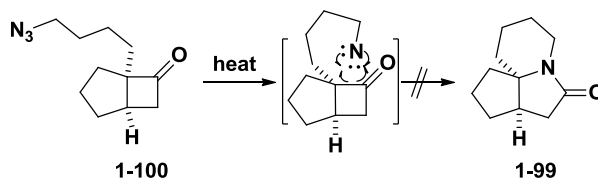
1.4.3 Results and discussion

Intramolecular Schmidt reaction. After the azide displacement, the intramolecular Schmidt reaction proceeded smoothly in high yield (Scheme 40).



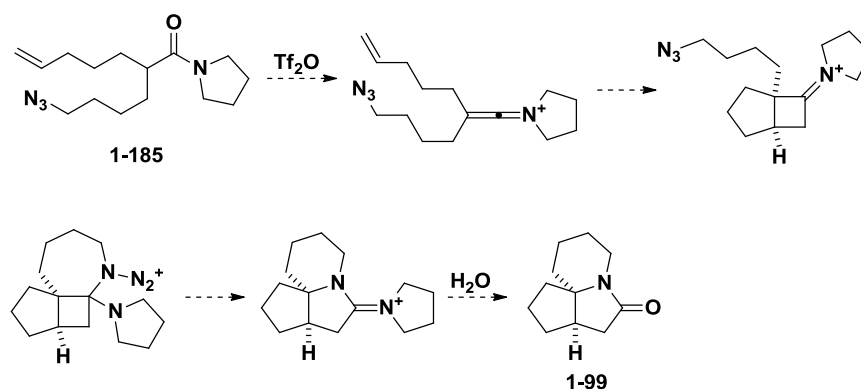
Scheme 40. Intramolecular Schmidt reaction.

We imagined that the bond between carbonyl group and cyclopentane is a bit weak due to the ring strain of cyclobutanone. In principle, nitrene could be formed under thermal conditions and the following insertion can give Schmidt product **1-99** (Scheme 41). However, attempted reactions under several conditions such as refluxing in chlorobenzene or the addition of catalytic amount of AIBN, known to facilitate the generation of nitrene, did not lead to **1-99**.



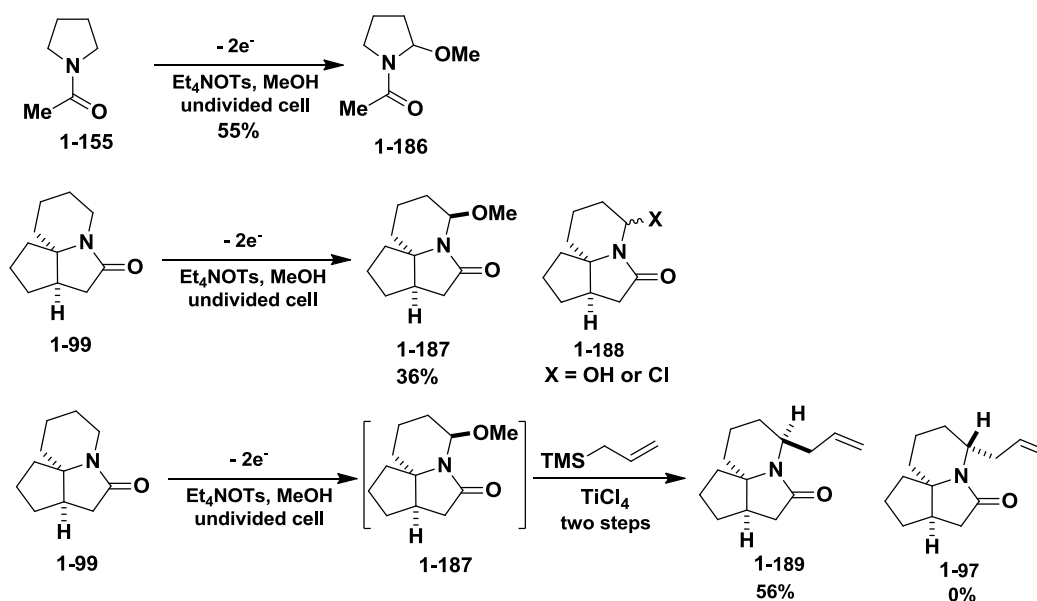
Scheme 41. Nitrene-mediated Schmidt reaction.

We also wanted to combine [2+2] cycloaddition with intramolecular reaction (Scheme 42). However, no good results were obtained. It is possible that the nitrogen in the azide group is a better nucleophile than the amide towards triflic anhydride, which may interfere with the [2+2] step.



Scheme 42. Proposed combination of [2+2] cycloaddition and Schmidt reaction.

Electrochemistry. The home-made electrochemistry apparatus was used to develop a general method to prepare complex acyliminium ion precursors. We first used amide **1-155** as the model system to optimize the conditions (Scheme 43). The acyliminium ion precursor **1-186** can be obtained in 55% yield. When the same condition was applied for tricyclic lactam **1-99**, compound **1-187** was obtained in 36% yield, along with other impurities of the general form **1-188** after silica gel column purification. When crude product **1-187** was used directly for the next allylation, compound **1-189** was obtained in 56% yield. However, the stereochemistry of the product was not suitable for advancement to pinnaic acid.



Scheme 43. Electrochemistry-mediated synthesis.

Acyliminium ion, generated from **1-187** under the Lewis acid conditions, has two conformations, each of which has two reactive pathways (Figure 30). One is through a chair-like transition state and the other a twist-boat like transition state. For conformation **A**, the allyl nucleophile attacks the acyliminium ion from top face to form chair-like TS, and leads to compound **1-189**. If the attack is from the bottom face, a twist-boat like transition state reacts to form **1-97**. For conformation **B**, a chair-like TS gives **1-97** and the twisted boat **1-189**. Because transition state energy is much higher for twist-boat than chair, the formation of major products should be from chair-like transition state. Then the distribution of products really depends on which conformation is more stable. For conformation **A**, the joint bond between cyclopentane and pyrrolidin-2-one ring lies on the pseudo-equatorial position. However, it is on the pseudo-axial position for conformation **B**. As shown in Figure 30, it is on the same plane for all the bonds connecting acyliminium ion. If the joint bond is at the pseudo-axial position, this makes the pyrrolidin-2-one ring very strained (dihedral angle is

pretty large). So the conformation **B** is less likely formed during the formation of acyliminium ion. Therefore, compound **1-189** is a major product.

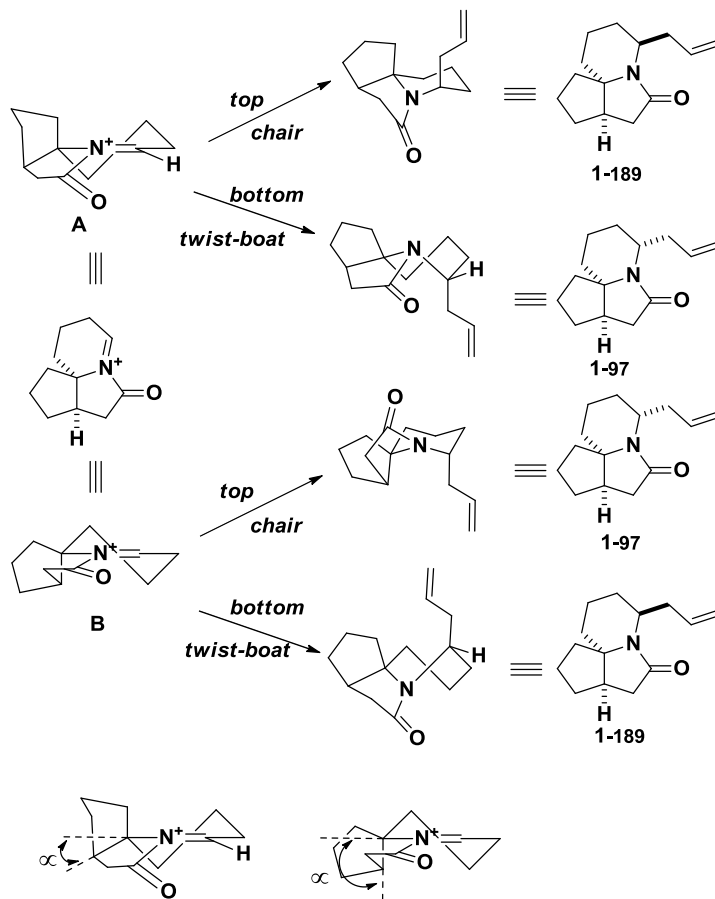


Figure 30. Mechanism for the allylation of N-acyliminium ion.

Due to the undesired stereochemistry based on our rationale, we imagined that the right stereochemistry could be obtained by the hydride attack of allylic acyliminium ion (Figure 31). The methoxy group of **1-187** was transferred to an electron-withdrawing group. This group must have the ability to make the α -H acidic, which could be deprotonated and alkylated with allyl bromide. This group also must be able to be released to form allyl acyliminium ion, which could be attacked by hydride from the top face to our desired product **1-97**.

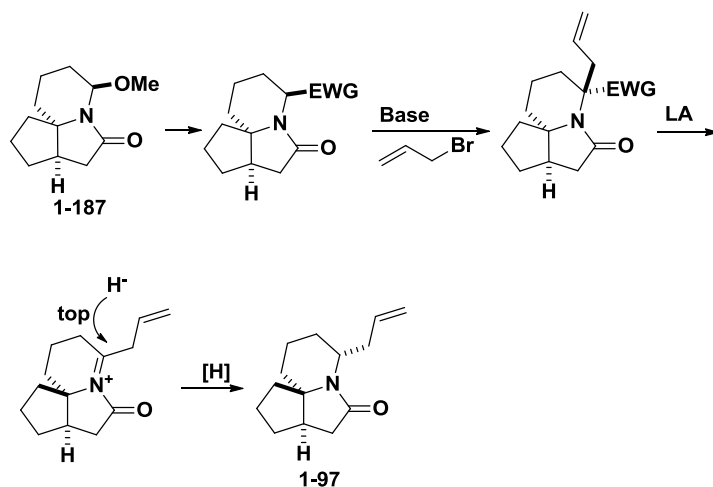
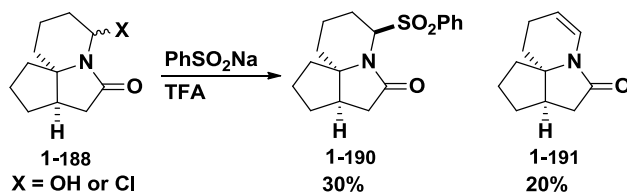


Figure 31. Strategy to modify the undesired stereochemistry of **1-187**.

The phenylsulfonyl group is initially used as the functional group to modify the undesired stereochemistry. However, we did not obtain the product in good yield when we tried to prepare it (Scheme 44). Maybe compound **1-190** is unstable during the silica gel column purification, and eliminated to **1-191**.



Scheme 44. Sulfonyl synthetic route.

After the determination of its relative stereochemistry, we found that the α hydrogen (as shown) is always at the pseudo-equatorial position and its ^1H chemical shift is a little higher than its β partner (Figure 32). This is due to the downfield H atom being placed in the deshielding area of the lactam carbonyl group.

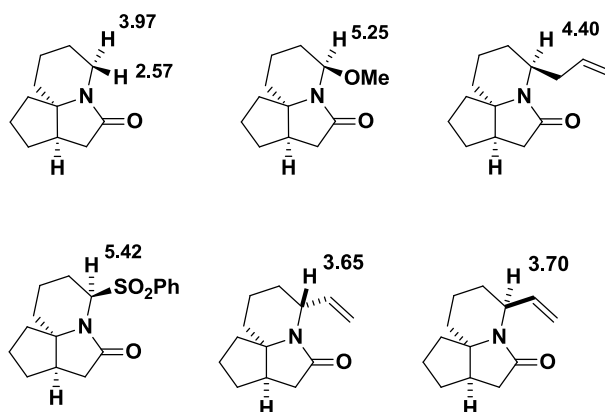
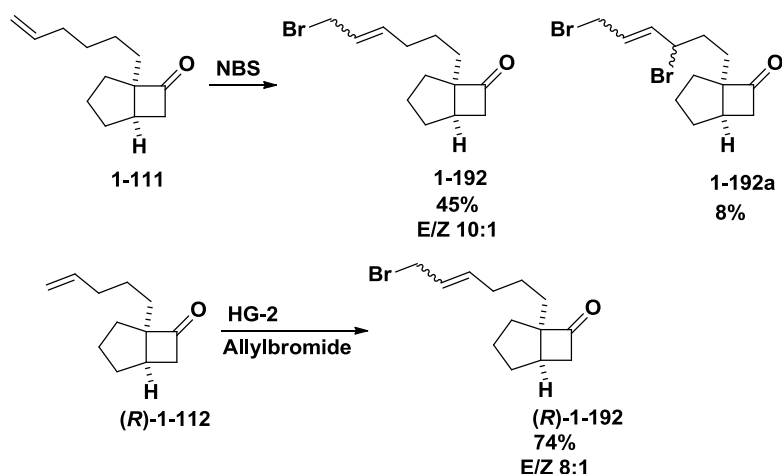


Figure 32. Spectral data of tricyclic lactams.

1.5 Allylic azide rearrangement/Schmidt-mediated synthesis towards pinnaic acid

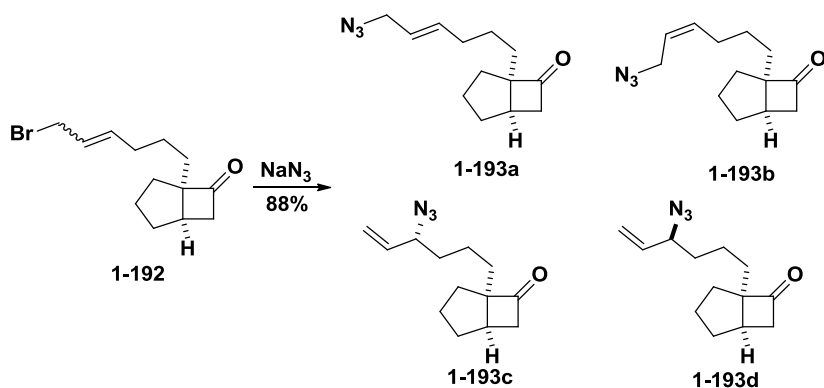
The combination of allylic azide rearrangement and intramolecular Schmidt reaction was initially considered as a solution to the pinnaic acid problem. However, we did not use this substrate for our initial studies of this sequence because this system belongs to the relatively unfavored 4-C tethered Schmidt reaction (azide is 4 carbons away from α -position of ketone). Chapter 2 details our initial studies of this combined reaction, which are not discussed in the pinnaic acid context below.

Preparation of allylic azides. Allylic azides could be prepared by azide displacement of the corresponding allylic bromides (Scheme 45). Allylic bromides were prepared by allylic bromination using NBS or cross-metathesis with allyl bromide. First, we used allylic bromination of cyclobutanone **1-111** to prepare bromide **1-192**, along with some di-brominated compound **1-192a**. After recognizing that cyclobutanone **1-111** could not be prepared in an enantiopure form, we investigated a route to bromide **1-192** via cross-metathesis, which gave product in a high *E/Z* ratio.



Scheme 45. Preparation of allylic bromide.

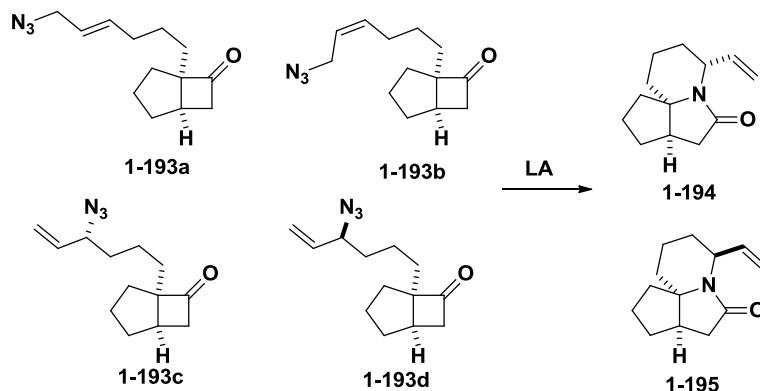
A mixture of isomeric allylic azides **1-193** was successfully obtained through azide displacement in 88% yield with 65:9:13:13 ratio from ^1H NMR in acetone (Scheme 46). Allylic azide rearrangement is facile at room temperature.



Scheme 46. Preparation of allylic azides.

Allylic azide rearrangement/intramolecular Schmidt reaction condition screening. First, we screened a variety of conditions to effect this transformation. We found 1.5 equiv TiCl_4 in refluxing dichloroethane to be the best condition, affording a 10:1 dr of products in 68% yield (Table 2). Although there are other minor products (<3%), the major products are our desired products **1-194** and **1-195**.

Table 2. Allylic azide rearrangement/intramolecular Schmidt reaction condition screening.



	Conditions	Yield	Ratio	Note
		(1-194+1-196)	(1-194:1-196)	
1	3 eq TiCl ₄ , DCM, rt	35%	5 : 2	
2	3 eq TiCl ₄ , toluene, 80 °C	35%	5:1	
3	3 eq BF ₃ ·OEt ₂ , DCM, -78 °C			decomposed
4	TFA, 0 °C			decomposed
5	3 eq SnCl ₄ , DCM, reflux			decomposed
6	1.5 eq TiCl ₄ , DCM, reflux	48%	4:1	
7	1.5 eq TiCl ₄ , CHCl ₃ , reflux	54%	10:1	
8	1.5 eq TiCl ₄ , DCE, reflux	68%	10:1	
9	1.5 eq TiCl ₄ , CCl ₄ , reflux	24%	8:1	
10	1.5 eq TiCl ₄ , toluene, reflux	41%	20:1	

After that, we attempted to rationalize our results. Based on the mechanism (Figure 33), there are two possible ring systems: normal amide and twisted amide, which result from the bond migration a or b respectively. Usually the formation of twisted amide needs specific conformation and higher energy. In this case, it should be tough to obtain the twisted amide.

There are also two possible nucleophilic attack pathways of azide to the carbonyl group of cyclobutanone: *syn* and *anti*. The azepane ring is flexible so that both pathways should be possible. We crudely calculated the possible intermediates, whose conformations as we thought could have minimum energies, using Chem-3D program through the minimized energy of MM2 calculations. The results showed that *anti*-attack needs ~3-5 kcal/mol higher than the corresponding *syn*-attack. As known in organic chemistry, the most stable conformation of cycloheptane ring is not the chair conformation because there are some eclipsing hydrogens. Actually for our case, the chair conformation is the most stable conformation for our case because of the fused cyclobutane ring, whose two C-C bonds are at the eclipsing position (Table 3). The calculated results indicated that conformation **B** is more stable than conformation **A**, which leads to lactam **1-194** as the major product. As shown in Figure 34, the interaction of endo-CH₂ in the cyclobutane ring with pseudo-axial hydrogen of azepane ring for conformation **A** is large, in comparison to the interaction of pseudo-axial CH₂ in the cyclopentane ring with pseudo-axial hydrogen of azepane ring for conformation **B**.

We also calculated the energies of two products using the same program (Table 3). We found that lactam **1-194** is not more stable than **1-195** although its vinyl group is at pseudo-equatorial position. Maybe there is some A^{1,3} strains between the carbonyl group and vinyl group in the molecular conformation of **1-194** (Figure 34). Although the vinyl group of **1-195** is at the pseudo-axial position, the computational results indicated that **1-195** is more stable.

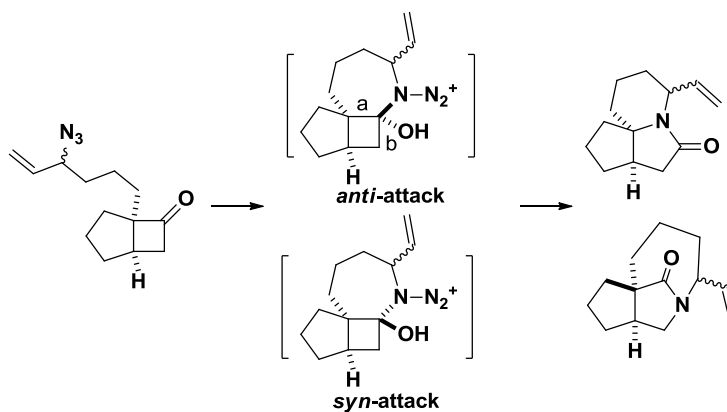
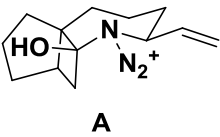
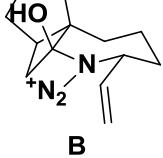
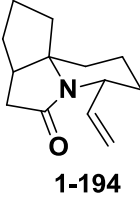
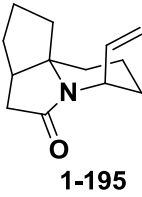
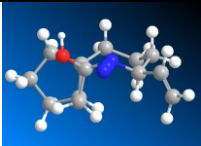
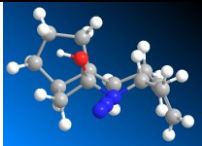
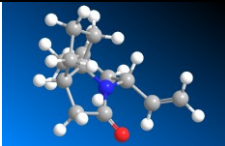
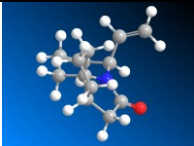


Figure 33. Mechanism of Schmidt reaction in the synthesis of pinnaic acid.

Table 3. Calculated results of intermediates in the Schmidt reaction.

Intermediate				
	A	B	1-194	1-195
Chem-3D model				
Cal. energy (kcal/mol)	54.3	51.1	22.4	21.5

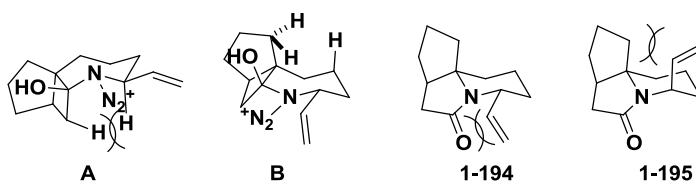
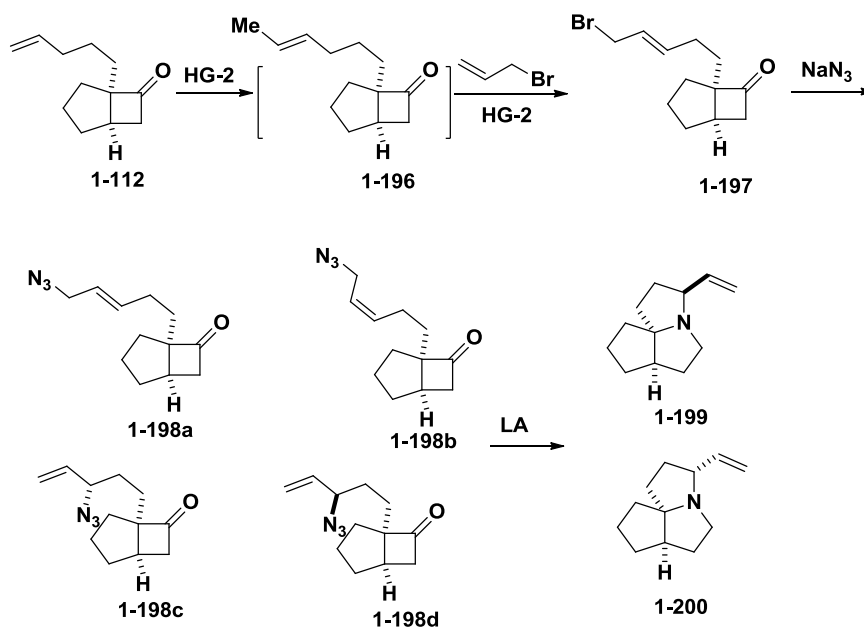


Figure 34. Steric interaction of intermediates and products.

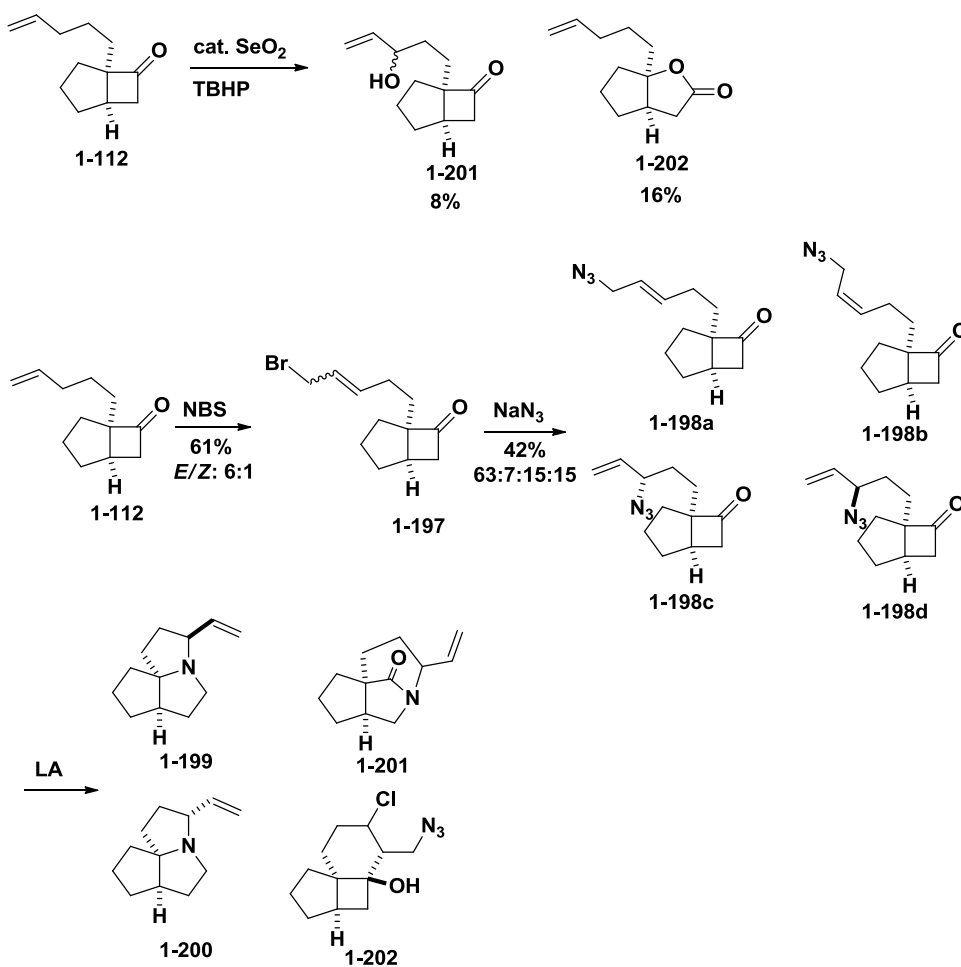
Studies of minor lactams. We also identified some minor products produced during the combined allylic azide rearrangement/Schmidt reaction. Our initial hypothesis was that the twisted amide was produced in this reaction (see chapter 2). After examining the detailed spectra, we speculated that maybe there is one carbon missed in the cross-metathesis. Ruthenium-H catalyst is known for this olefin isomerization.⁶² Grubbs catalysts are also known to convert an *O*- or *N*-allyl substrate to an *O*- or *N*-propenyl product.⁶³ It was reported that the isomerized substrate for all-carbon substrate is the minor product during the cross-metathesis using Grubbs catalysts.⁶² This would explain how we could get a mixture of one-carbon less Schmidt product through the whole process shown in Scheme 47.



Scheme 47. Grubbs catalyst mediated isomerization.

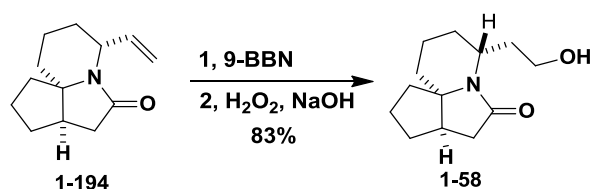
We next tried to synthesize those Schmidt products directly to further confirm this speculation (Scheme 48). Starting from cyclobutanone **1-112**, we tested the allylic oxidation conditions to get allylic alcohol **1-201**; however, the yield was low. Then we turned to allylic bromination to get allylic bromide **1-197**; the product was obtained in 61% yield. The

following azide displacement afforded a mixture of interconverted allylic azides in 42% yield. The combined allylic azide rearrangement and intramolecular Schmidt reaction was accomplished using TiCl_4 in refluxing dichloromethane. However, this reaction is much more complex than the homologous reaction. We suspected that the reaction mixture contained twisted amides and halo-Prins side products (the latter will be discussed thoroughly in Chapter 2). Fortunately, compounds **1-199** and **1-200** were isolated and confirmed to be the minor products during the preparation of lactam **1-194**, as expected.



Scheme 48. Preparation of lactams **1-199** and **1-200**.

To complete the formal synthesis, the final step was achieved using a hydroboration/oxidation reaction in 83% yield (Scheme 49). Thus, we have achieved a formal synthesis of natural product pinnaic acid. We also compared our spectral data with the values reported by Kibayashi (Table 4 and Table 5).¹⁵



Scheme 49. End-game reaction.

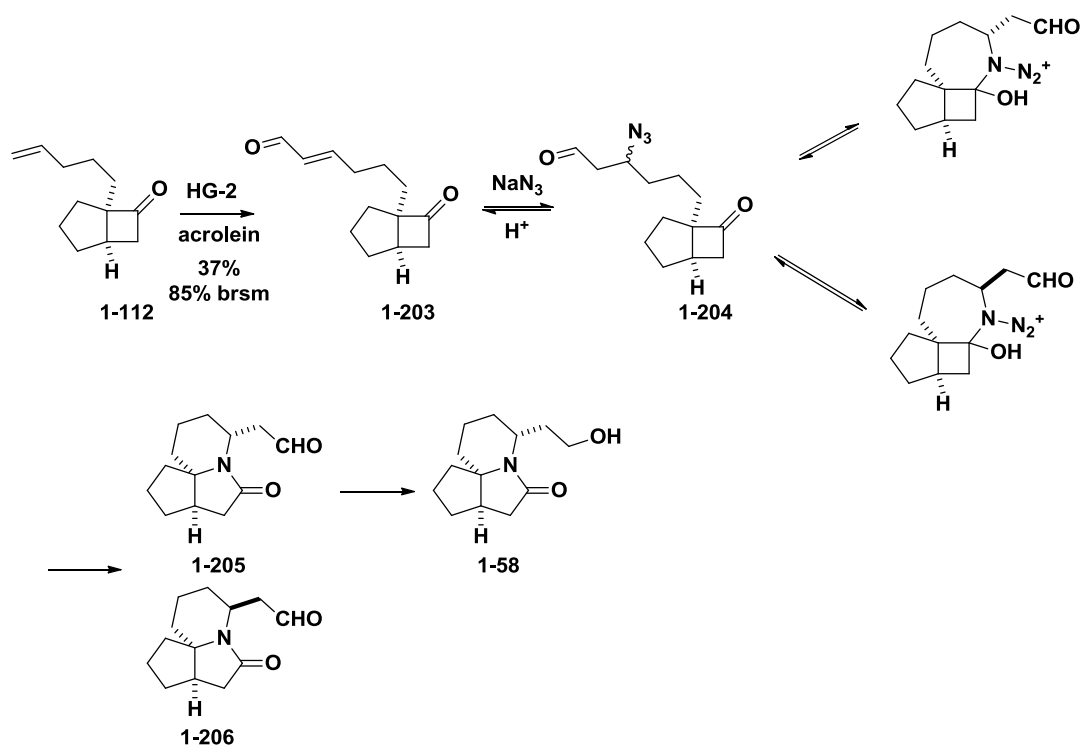
Table 4. Comparison table of ¹H NMR characterization data.

Found	Reference ¹⁵
3.72-3.79 (m, 2H)	3.65-3.75 (m, 2H)
3.29-3.34 (m, 1H)	3.24-3.30 (br m, 1H)
3.00 (br s, 1H)	3.13 (br s, 1H)
2.84-2.93 (m, 1H)	2.79-2.88 (m, 1H)
2.65 (dd, <i>J</i> = 18.0 Hz, 10.4 Hz, 1H)	2.60 (dd, <i>J</i> = 18.0 Hz, 10.3 Hz, 1H)
2.07-2.17 (m, 2H)	2.02-2.11 (m, 2H)
1.79-2.00 (m, 4H)	1.74-1.94 (m, 4H)
1.69-1.77 (m, 1H)	1.63-1.72 (m, 1H)
1.57-1.67 (m, 5H)	1.56-1.64 (m, 5H)
1.35-1.57 (m, 3H)	1.38-1.57 (m, 2H)
	1.30-1.39 (m, 1H)

Table 5. Comparison table of ^{13}C NMR characterization data.

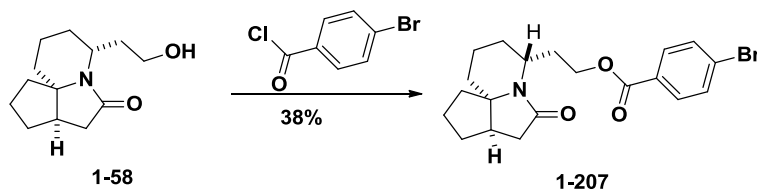
Found	Reference ¹⁵	Δ value
174.28 (C)	174.13	0.15
74.09 (C)	73.99	0.10
60.97 (CH ₂)	60.76	0.21
53.74 (CH)	53.56	0.18
42.04 (CH)	41.99	0.05
38.48 (CH ₂)	38.40	0.08
36.49 (CH ₂)	36.46	0.03
35.45 (CH ₂)	35.37	0.08
34.92 (CH ₂)	34.90	0.02
33.65 (CH ₂)	33.62	0.03
32.15 (CH ₂)	32.04	0.11
25.21 (CH ₂)	25.16	0.05
22.50 (CH ₂)	22.49	0.01

We also imagined that alcohol **1-58** could be made through the combination of aza-Michael addition and intramolecular Schmidt reaction (Scheme 50). The α,β -unsaturated aldehyde was prepared by cross-metathesis in 37% yield. We tried several conditions to combine the aza-Michael addition and intramolecular Schmidt reactions, however, without success.



Scheme 50. The combination of aza-Michael addition and Schmidt reactions.

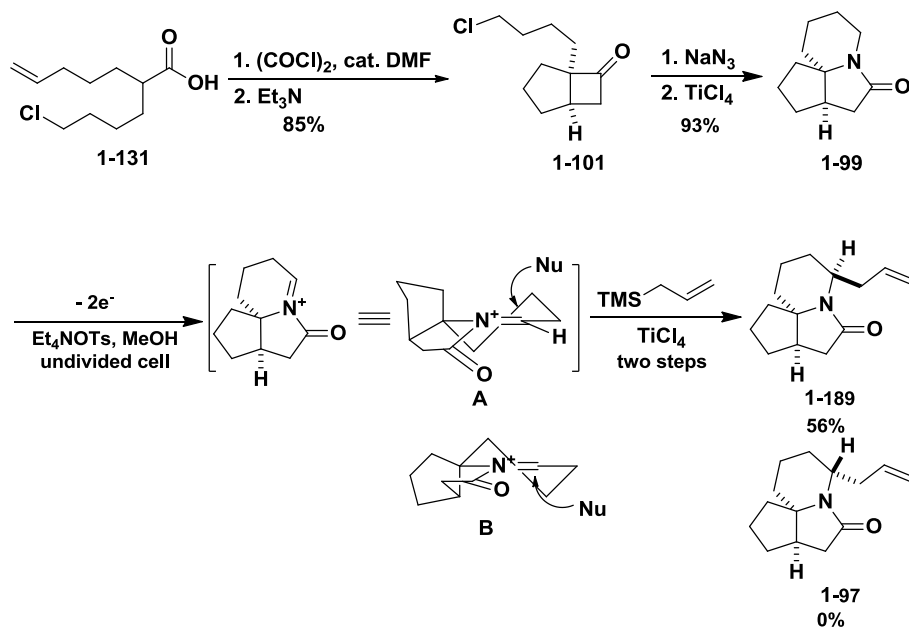
Determination of absolute configuration. Since we were not able to establish the absolute configuration at the cyclobutanone stage, we attempted derivatization of the penultimate compound. We still relied on heavy-atom assisted crystallography technique to determine the absolute configuration through esterification with 4-bromobenzoyl chloride (Scheme 51). Unfortunately, ester **1-207** was not crystalline, and better results may have been found using carbamates or nitrobenzoyl analogue.



Scheme 51. Esterification of alcohol 1-58.

1.6 Conclusion

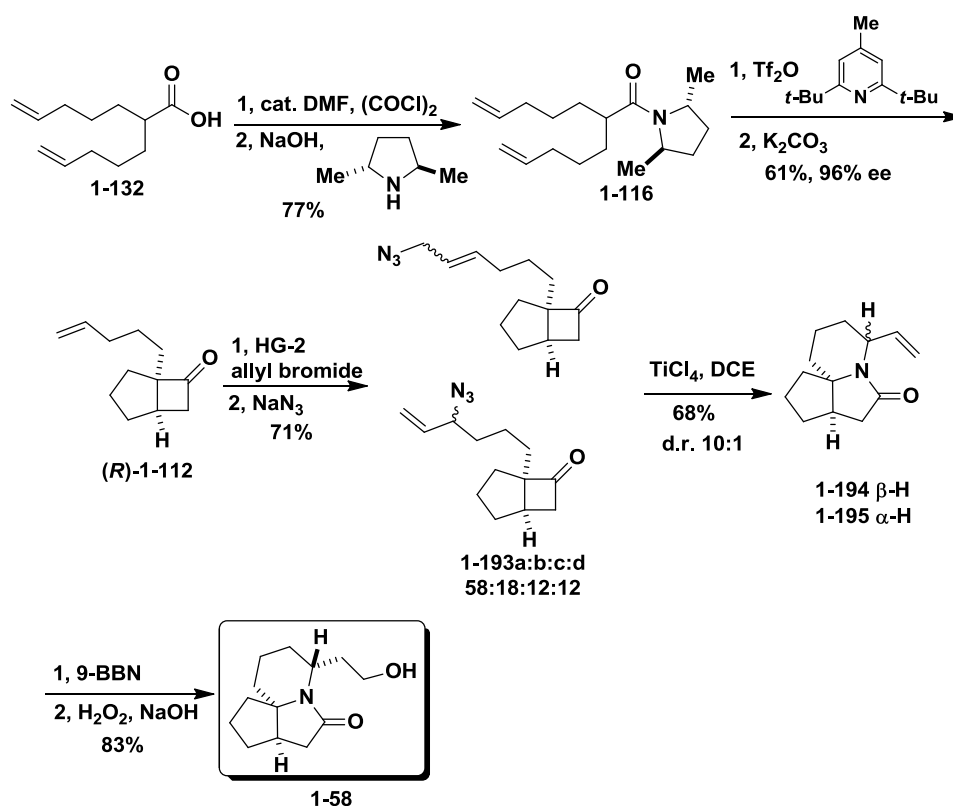
We carried out the studies toward the synthesis of advanced intermediates of the natural product pinnaic acid. In one approach, an electrochemistry mediated manipulation of an intramolecular Schmidt product was utilized to synthesize the advanced intermediate, tricyclic lactam **1-97** (Scheme 52). A ketene-mediated [2+2] cycloaddition was used to get intramolecular Schmidt starting material, which afforded un-modified tricyclic lactam. Utilizing anodic oxidation, this lactam was modified to give an acyliminium ion, which was attacked by nucleophiles to give allylated tricyclic lactam **1-189**. Unfortunately, product with the undesired stereochemistry was obtained. From another perspective, this sequence is complementary to the discovery in the combination of allylic azide rearrangement and intramolecular Schmidt reaction, and both methods can afford epimeric tricyclic lactams.



Scheme 52. Electrochemistry-mediated synthesis towards pinnaic acid.

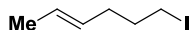
The synthesis of an advanced intermediate of pinnaic acid was ultimately achieved by the combination of allylic azide rearrangement and intramolecular Schmidt reaction

(Scheme 53). An enantioselective [2+2] cycloaddition was accomplished under the assistance of chiral amine to afford product of 96% ee in 61% yield. The following cross-metathesis and azide displacement afforded a mixture of interconverting allylic azides, whose rearrangement is facile at room temperature. The combination of allylic azide rearrangement and intramolecular Schmidt reaction was accomplished to give tricyclic lactam **1-194** with 10:1 dr in 68% yield following a screening of reaction conditions. The formal synthesis was finished by the hydroboration and oxidation sequence to give the reported advanced intermediate.

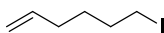


Scheme 53. Asymmetric [2+2] cycloaddition involved synthesis of advanced intermediate.

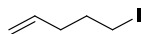
1.7 Experimental data



(E)-6-Iodo-2-hexene. Following the reported procedure,⁶⁴ to a solution of (E)-4-hexen-1-ol (1.0 g, 10 mmol) and Et₃N (1.6 g, 15 mmol) in CH₂Cl₂ (30 mL) at 0 °C under Ar atmosphere was added dropwise methane sulfonylchloride (1.26 g, 11.0 mmol). The solution was stirred overnight. The resulting solution was diluted with CH₂Cl₂ (30 mL), washed successively with HCl (0.5 M, 35 mL), saturated aqueous NaHCO₃ (75 mL), and H₂O (2 × 75 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo to give the crude mesylate as an oil (2.4 g). The mesylate was added to a solution of NaI (4.25 g, 25.0 mmol) in acetone (30 mL) and heated to reflux overnight. After cooling to room temperature, the reaction mixture was diluted with hexane (50 mL), washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo to give pure (E)-6-iodo-2-hexene (1.71 g, 82%) as a colorless oil. The spectral data matched with reported data.⁶⁴

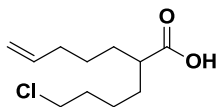


6-Iodo-1-hexene. According to the procedure described for (E)-6-iodo-2-hexene, 5-hexen-1-ol (12.5 g, 125 mmol) afforded 6-iodo-1-hexene (28.0 g, 107%) as a colorless oil. The spectral data matched with reported data.⁶⁵

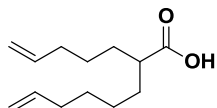


5-Iodo-1-pentene. Following the reported procedure,⁶⁶ to a solution of 5-bromo-1-pentene (11.6 g, 77.9 mmol) in dry acetone (200 mL) was added sodium iodide (23.2 g, 156 mmol). The reaction mixture was stirred and heated at reflux for 3.5 h. The reaction mixture was cooled to room temperature; pentane and water were added. The phases were separated, and the organic phase was extracted with pentane. The combined organic phases were washed with brine and dried over anhydrous sodium sulfate. After filtration and removal of

solvent at reduced pressure, 5-iodo-1-pentene was obtained (14.0 g, 92%) as a colorless oil, which was used in the next synthetic step without further purification. The spectral data matched with reported data.⁶⁶

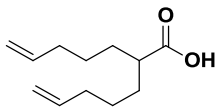


2-(4-Chlorobutyl)hept-6-enoic acid (1-129).³⁸ According to the procedure described for 2-(pent-4-en-1-yl)oct-7-enoic acid (**1-153**), hept-6-enoic acid (**1-152**) (1.02 g, 8.00 mmol) and 1-bromo-4-chlorobutane (1.65 g, 9.60 mmol) afforded after chromatography acid **1-129** (1.20 g, 69%) as a colorless oil. Acid **1-129**: R_f = 0.35 (20% EtOAc/hexanes); IR (neat) 3071, 2942, 1702, 1286 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{37}\text{Cl}_2\text{O}_4$ (2M-H)⁺ 435.2069, found: 435.2035; ^1H NMR (400 MHz, CDCl_3) δ 1.42-1.55 (m, 6H), 1.63-1.73 (m, 2H), 1.76-1.83 (m, 2H), 2.08 (q, J = 7.2 Hz, 2H), 2.35-2.42 (m, 1H), 3.54 (t, J = 6.8 Hz, 2H), 4.96-5.05 (m, 2H), 5.75-5.82 (m, 1H), 11.07 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.7 (CH_2), 26.5 (CH_2), 31.3 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 33.5 (CH_2), 44.7 (CH_2), 45.3 (CH), 114.8 (CH_2), 138.3 (CH), 182.8 (C).

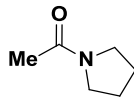


2-(Pent-4-en-1-yl)oct-7-enoic acid (1-153). Following the reported procedure,²⁷ *n*-BuLi (2.3M in hexane, 8.0 mL, 18.4 mmol) was slowly added to a solution of diisopropylamine (1.92 g, 19.0 mmol) in THF (20 mL) at 0 °C under N_2 atmosphere. After 1 h at 0 °C, a precooled solution of hept-6-enoic acid (0.836 g, 6.53 mmol) and DMPU (2.0 g, 16 mmol) in THF (10 mL) was slowly added. After 1.5 h at room temperature, 6-iodo-1-hexene (1.98 g, 9.40 mmol) was slowly added. The resulting mixture was warmed slowly to room temperature and stirring overnight. Saturated ammonium chloride was used to quench

the reaction. After separation, the aqueous layer was washed with ethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed (5-50% EtOAc/hexanes) to yield acid **1-153** (1.12 g, 68%) as a colorless oil. Acid **1-153**: $R_f = 0.20$ (100% EtOAc/hexanes); IR (neat) 2932, 1705 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{21}\text{O}_2$ (M-H) $^-$ 209.1542, found: 209.1597; ^1H NMR (400 MHz, CDCl_3) δ 1.41-1.58 (m, 8H), 1.63-1.70 (m, 2H), 2.03-2.09 (m, 4H), 2.35-2.41 (m, 1H), 4.95-5.06 (m, 4H), 5.77-5.85 (m, 2H), 11.15 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.6 (CH_2), 26.8 (CH_2), 28.8 (CH_2), 31.5 (CH_2), 31.9 (CH_2), 33.5 (CH_2), 33.6 (CH_2), 45.4 (CH), 114.4 (CH_2), 114.7 (CH_2), 138.4 (CH), 138.7 (CH), 182.9 (C).

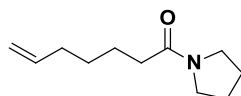


2-(Pent-4-en-1-yl)hept-6-enoic acid (1-132).³⁹ According to the procedure described for 2-(pent-4-en-1-yl)oct-7-enoic acid (**1-153**), hept-6-enoic acid (**1-152**) (1.90 g, 14.8 mmol) and 5-iodo-1-pentene (2.94 g, 15.0 mmol) afforded after chromatography acid **1-132** (1.66 g, 57%) as a colorless oil. Acid **1-132**: $R_f = 0.35$ (20% EtOAc/hexanes); IR (neat) 2940, 1705, 911 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.47-1.58 (m, 6H), 1.64-1.74 (m, 2H), 2.08 (q, $J = 6.8$ Hz, 4H), 2.35-2.43 (m, 1H), 4.96-5.06 (m, 4H), 5.76-5.86 (m, 2H), 11.52 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.6 (CH_2), 31.5 (CH_2), 33.6 (CH_2), 45.3 (CH), 114.8 (CH_2), 138.4 (CH), 182.7 (C).



1-(Pyrrolidin-1-yl)ethanone (1-155). To a suspension of pyrrolidine (7.1 g, 10 mmol) in a mixed solvent of dichloromethane (50 mL) and aqueous NaOH (1 M, 30 mL) at 0 $^{\circ}\text{C}$ under N_2 atmosphere was added dropwise a solution of acetyl chloride (12 g, 15 mmol)

in dichloromethane (15 mL). The resulting mixture was stirred for 3 h. After separation, the aqueous layer was extracted with dichloromethane twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The concentration afforded pure amide **1-155** (7.4 g, 65%) as a colorless oil. The spectral data matched with reported data.⁶⁷

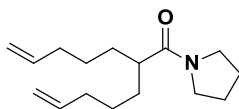


1-(Pyrrolidin-1-yl)hept-6-en-1-one (1-154).

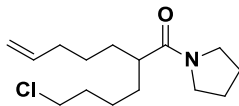
Method I: To a solution of hept-6-enoic acid (**1-152**) (0.85 g, 6.6 mmol) in dichloromethane (100 mL) at 0 °C under N₂ atmosphere was added one drop of DMF, followed by the dropwise addition of oxalyl chloride (1.3 mL, 20 mmol). The resulting mixture was stirred at 0 °C for 0.5 h and at room temperature for 2 h. The solvent was removed in rotovap. The residue was dissolved in dichloromethane (100 mL), followed by the slow addition of pyrrolidine (1.42 g, 20.0 mmol). The resulting mixture was stirred overnight, and then washed successively with 1 M HCl, 1 M NaOH, and brine, dried over anhydrous sodium sulfate. Concentration afforded amide **1-154** (1.25 g, 100%) as a colorless oil.

Method II: To a solution of 1-(pyrrolidin-1-yl)ethanone (**1-155**) (3.4 g, 30 mmol) in THF (80 mL) at -78 °C under N₂ atmosphere was added freshly prepared LDA (1 M, 36 mL, 36 mmol). After 0.5 h at -78 °C, 5-bromo-1-pentene (5.4 g, 36 mmol) was slowly added. The resulting mixture was slowly warmed to room temperature in 2 h. Saturated ammonium chloride was used to quench the reaction. After separation, the aqueous layer was washed with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed (5-50% EtOAc/hexanes) to yield amide **1-154** (4.3 g, 79%) as a colorless oil and 2-(pent-4-en-1-yl)-

1-(pyrrolidin-1-yl)hept-6-en-1-one (0.7 g, 9%) as a colorless oil. Amide **1-154**: R_f = 0.25 (50% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 1.41-1.49 (m, 2H), 1.63-1.72 (m, 2H), 1.81-1.89 (m, 2H), 1.92-1.99 (m, 2H), 2.05-2.12 (m, 2H), 2.27 (t, J = 7.2 Hz, 2H), 3.41 (t, J = 6.8 Hz, 2H), 3.46 (t, J = 6.9 Hz, 2H), 4.94 (ddt, J = 10.2, 2.1, 1.2 Hz, 1H), 5.01 (dq, J = 17.1, 1.7 Hz, 1H), 5.81 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.4, 24.4, 26.1, 28.8, 33.6, 34.6, 45.6, 46.60, 114.5, 138.7, 171.6.

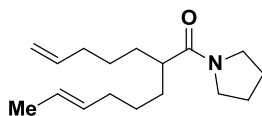


2-(Pent-4-en-1-yl)-1-(pyrrolidin-1-yl)hept-6-en-1-one. R_f = 0.35 (50% EtOAc/hexanes); IR (neat) 2929, 1640, 1444 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{16}\text{H}_{28}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 250.2171, found: 250.2181; ^1H NMR (400 MHz, CDCl_3) δ 1.30-1.50 (m, 6H), 1.63-1.72 (m, 2H), 1.81-1.90 (m, 2H), 1.95 (q, J = 6.4 Hz, 2H), 2.00-2.08 (m, 4H), 2.48 (tt, J = 9.1, 4.9 Hz, 1H), 3.49 (q, J = 7.1 Hz, 4H), 4.95 (ddd, J = 10.2, 2.0, 1.0 Hz, 1H), 5.00 (dq, J = 17.1, 1.6 Hz, 1H), 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 24.4, 26.2, 27.0, 32.5, 34.0, 43.8, 45.6, 46.7, 114.5, 138.7, 174.7.

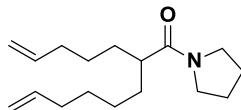


2-(4-Chlorobutyl)-1-(pyrrolidin-1-yl)hept-6-en-1-one (1-131).³⁸ To a solution of amide **1-154** (625 mg, 3.50 mmol) in THF (30 mL) at $-78\text{ }^\circ\text{C}$ under N_2 atmosphere was added freshly prepared LDA (1.0 M, 4.9 mL, 4.9 mmol). After 2 h at $-78\text{ }^\circ\text{C}$, 1-bromo-4-chlorobutane (720 mg, 4.20 mmol) was slowly added. The resulting mixture was slowly warmed to room temperature and stirring overnight. Saturated ammonium chloride was used to quench the reaction. After separation, the aqueous layer was washed with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous

sodium sulfate, and concentrated. The residue was chromatographed (5-50% EtOAc/hexanes) to yield amide **1-131** (670 mg, 83%) as a colorless oil. Amide **1-131**: R_f = 0.65 (100% EtOAc/hexanes); IR (neat) 2936, 1638, 1432 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{15}\text{H}_{27}\text{ClNO}$ ($\text{M}+\text{H}$)⁺ 272.1781, found: 272.1779; ^1H NMR (400 MHz, CDCl_3) δ 1.31-1.50 (m, 6H), 1.62-1.73 (m, 2H), 1.74-1.82 (m, 2H), 1.85-1.91 (m, 2H), 1.93-1.99 (m, 2H), 2.00-2.09 (m, 2H), 2.49 (tt, J = 9.4, 4.7 Hz, 1H), 3.46-3.59 (m, 6H), 4.92-4.97 (m, 1H), 5.00 (dq, J = 17.2, 1.6 Hz, 1H), 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.4, 25.0, 26.2, 26.9, 32.1, 32.5, 32.8, 33.9, 43.8, 45.0, 45.6, 46.7, 114.6, 138.6, 174.4.

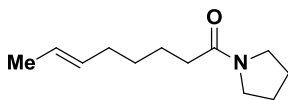


(E)-2-(Pent-4-en-1-yl)-1-(pyrrolidin-1-yl)oct-6-en-1-one (1-156). According to the procedure described for amide **1-131**, amide **1-154** (363 mg, 2.00 mmol) and (*E*)-6-Iodo-2-hexene (465 g, 2.20 mmol) afforded after chromatography amide **1-156** (475 mg, 85%) as a colorless oil. Amide **1-156**: R_f = 0.55 (50% EtOAc/hexanes); HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{30}\text{NO}$ ($\text{M}+\text{H}$)⁺ 264.2327, found: 264.2320; ^1H NMR (400 MHz, CDCl_3) δ 1.24-1.49 (m, 6H), 1.58-1.72 (m, 5H), 1.80-1.91 (m, 2H), 1.91-2.00 (m, 4H), 2.00-2.09 (m, 2H), 2.46 (tt, J = 9.0, 5.0 Hz, 1H), 3.49 (dt, J = 8.6, 6.9 Hz, 4H), 4.94 (ddt, J = 10.2, 2.1, 1.1 Hz, 1H), 5.00 (dq, J = 17.1, 1.6 Hz, 1H), 5.37-5.44 (m, 2H), 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.9, 24.4, 26.2, 27.0, 27.7, 32.5, 32.6, 32.8, 34.0, 43.8, 45.56, 46.7, 114.5, 125.0, 131.1, 138.7, 174.7.

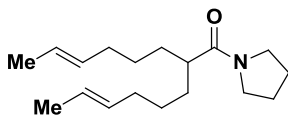


2-(Pent-4-en-1-yl)-1-(pyrrolidin-1-yl)oct-7-en-1-one (1-157). According to the procedure described for amide **1-131**, amide **1-154** (625 mg, 3.50 mmol) and 6-iodo-1-hexene

(700 mg, 4.20 mmol) afforded after chromatography amide **1-157** (470 mg, 52%) as a colorless oil. Amide **1-157**: R_f = 0.35 (50% EtOAc/hexanes); IR (neat) 2928, 1639, 1437 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{30}\text{NO}$ ($\text{M}+\text{H}$)⁺ 264.2327, found: 264.2320; ^1H NMR (400 MHz, CDCl_3) δ 1.21-1.49 (m, 8H), 1.60-1.71 (m, 2H), 1.80-1.90 (m, 2H), 1.91-1.99 (m, 2H), 2.00-2.08 (m, 4H), 2.41-2.50 (m, 1H), 3.48 (q, J = 7.0 Hz, 4H), 4.91-4.95 (m, 2H), 4.95-5.02 (m, 2H), 5.73-5.84 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.4, 26.2, 27.0, 27.2, 29.1, 32.5, 32.8, 33.7, 34.0, 43.9, 45.6, 46.7, 114.3, 114.5, 138.9, 138.9, 174.8.

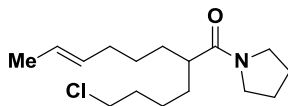


(E)-1-(Pyrrolidin-1-yl)oct-6-en-1-one (1-158). According to the procedure described for amide **1-131**, amide **1-155** (625 mg, 3.50 mmol) and (*E*)-6-iodo-2-hexene (3.15 g, 15.0 mmol) afforded after chromatography amide **1-158** (680 mg, 35%) and amide **1-159** (870 mg, 31%) as a colorless oil. Amide **1-158**: R_f = 0.25 (50% EtOAc/hexanes); HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{22}\text{NO}$ ($\text{M}+\text{H}$)⁺ 196.1701, found: 196.1682; ^1H NMR (400 MHz, CDCl_3) δ 1.35-1.45 (m, 2H), 1.59-1.70 (m, 5H), 1.86 (q, J = 6.6 Hz, 2H), 1.96 (q, J = 6.6 Hz, 2H), 2.22-2.29 (m, 2H), 3.41 (t, J = 6.8 Hz, 2H), 3.47 (t, J = 6.8 Hz, 2H), 5.40-5.44 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.9, 24.4, 24.5, 26.1, 29.4, 32.4, 34.7, 45.6, 46.6, 125.0, 131.1, 171.8.

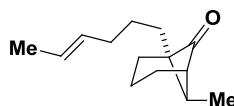


(E)-2-((E)-Hex-4-en-1-yl)-1-(pyrrolidin-1-yl)oct-6-en-1-one (1-159). Amide **1-159**: R_f = 0.50 (50% EtOAc/hexanes); HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{32}\text{NO}$ ($\text{M}+\text{H}$)⁺ 278.2484, found: 278.2441; ^1H NMR (400 MHz, CDCl_3) δ 1.25-1.36 (m, 4H), 1.37-1.47 (m, 2H), 1.57-1.69 (m, 8H), 1.81-1.90 (m, 2H), 1.90-2.01 (m, 6H), 2.45 (tt, J = 8.9, 5.0 Hz, 1H),

3.45-3.51 (m, 4H), 5.38-5.43 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.9, 24.4, 26.2, 27.7, 32.6, 32.8, 43.8, 45.6, 46.7, 125.0, 131.1, 174.8.

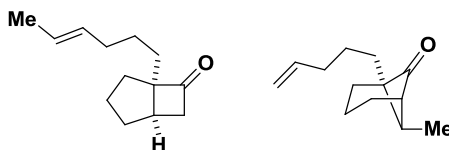


(E)-2-(4-Chlorobutyl)-1-(pyrrolidin-1-yl)oct-6-en-1-one. According to the procedure described for amide **1-131**, amide **1-156** (391 mg, 2.00 mmol) and 4-bromo-1-chlorobutane (380 mg, 2.2 mmol) afforded after chromatography the title amide (335 mg, 82% brsm) and amide **1-156** (113 mg) as a colorless oil. The title amide: R_f = 0.60 (100% EtOAc/hexanes); HRMS (ESI) m/z calculated for $\text{C}_{16}\text{H}_{29}\text{ClNO}$ ($\text{M}+\text{H}$) $^+$ 286.1938, found: 286.1921; ^1H NMR (400 MHz, CDCl_3) δ 1.23-1.35 (m, 2H), 1.36-1.49 (m, 4H), 1.56-1.71 (m, 5H), 1.72-1.82 (m, 2H), 1.82-1.92 (m, 2H), 1.92-2.01 (m, 4H), 2.47 (tt, J = 9.1, 4.9 Hz, 1H), 3.45-3.58 (m, 6H), 5.34-5.46 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.9, 24.4, 25.0, 26.2, 27.6, 32.1, 32.6, 32.8, 43.8, 45.0, 45.6, 46.7, 125.1, 131.0, 174.5.



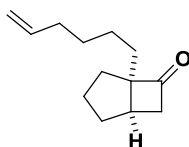
(1S*, 5R*, 7R*)-1-((E)-Hex-4-en-1-yl)-7-methylbicyclo[3.1.1]heptan-6-one (1-160). To a solution of amide **1-159** (726 mg, 2.60 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.23 g, 6.02 mmol) in anhydrous 1,2-dichloroethane (20 mL) under N_2 atmosphere at reflux was added dropwise a solution of triflic anhydride (1.47 g, 5.20 mmol) in anhydrous 1,2-dichloroethane (10 mL) over a period of 16 h using syringe pump. After the addition, the resulting mixture was allowed to reflux for additional 30 h. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. Carbon tetrachloride (25 mL) and water (25 mL) were added and the mixture was heated to reflux for 6 h. The resulting mixture was cooled to room temperature and two phases separated. The organic

phase was dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (1-5% EtOAc/hexanes) to afford cyclobutanone **1-160** (210 mg, 39%) as a colorless oil. Cyclobutanone **1-160**: R_f = 0.25 (5% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 1.00 (d, J = 6.8 Hz, 3H), 1.18-1.30 (m, 1H), 1.38-1.48 (m, 3H), 1.56-1.64 (m, 1H), 1.63-1.67 (m, 3H), 1.74-1.84 (m, 1H), 1.92-2.00 (m, 3H), 2.07 (ddd, J = 12.9, 7.7, 3.6 Hz, 1H), 2.22-2.33 (m, 3H), 2.60 (t, J = 3.2 Hz, 1H), 5.37-5.46 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 14.6, 17.9, 18.9, 23.6, 28.0, 33.1, 33.3, 35.8, 38.6, 62.1, 67.5, 125.2, 131.0, 215.4.



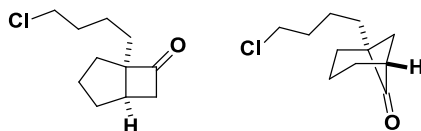
(1*R, 5*S**)-5-((*E*)-Hex-4-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-109)** and **(1*S**, 5*R**, 7*R**)-1-(pent-4-enyl)-7-methylbicyclo[3.1.1]heptan-6-one (1-162)**. To a solution of amide **1-156** (432 mg, 1.65 mmol) and collidine (242 mg, 2.00 mmol) in anhydrous 1,2-dichloroethane (17 mL) under N_2 atmosphere at reflux was added dropwise a solution of triflic anhydride (508 mg, 1.80 mmol) in anhydrous 1,2-dichloroethane (5 mL) over a period of 2 h using a syringe pump. After addition, the resulting mixture was allowed to reflux for additional 24 h. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. Carbon tetrachloride (20 mL) and water (20 mL) were added and the mixture was heated to reflux for 7 h. The resulting mixture was cooled to room temperature, aqueous HCl (1 M, 2 mL, 2 mmol) was added and two phases were separated. The organic phase was dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (1-5% EtOAc/hexanes) to afford a mixture of cyclobutanone **1-109** and **1-162** (2:1 ratio, 131 mg, 41%, 62% brsm) as a colorless oil and amide **1-156** (142 mg). Cyclobutanone **1-109** (diagnostic peaks only): R_f = 0.45 (5% EtOAc/hexanes); ^1H NMR (400

MHz, CDCl₃) δ 1.63-1.68 (m, 3H), 2.44 (dd, J = 18.4, 4.5 Hz, 1H), 2.58-2.62 (m, 1H), 3.12 (dd, J = 18.4, 9.5 Hz, 1H), 5.35-5.46 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 62.1, 67.4, 125.2, 130.9. Cyclobutanone **1-162** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 1.00 (d, J = 6.8 Hz, 3H), 2.55-2.59 (m, 1H), 4.97 (ddt, J = 10.2, 2.2, 1.2 Hz, 2H), 5.02 (dq, J = 17.1, 1.6 Hz, 1H), 5.81 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 114.7, 138.5.



(1R*, 5R*)-5-(Hex-5-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-111). To a solution of 2-(pent-4-en-1-yl)oct-7-enoic acid (**1-153**) (0.95 g, 4.5 mmol) and one drop of DMF (2 drops) in benzene (15 mL) at 0 °C under N₂ atmosphere was dropwise added oxalyl chloride (2.30 mL, 26.5 mmol). After 0.5 h at room temperature, the reaction mixture was heated to reflux for 1.5 h. After the reaction was cooled to room temperature, the solvent and excess oxalyl chloride was removed under reduced pressure. Toluene (10 mL) was added and removed again. This procedure was repeated twice. To a refluxing solution of triethylamine (4.5 mL, 32 mmol) in toluene (50 mL) under N₂ atmosphere was added dropwise a solution of the above residue in toluene (10 mL) using a syringe pump over 2 h. After the addition, the reaction mixture was allowed to reflux for another 24 h. After the reaction mixture was cooled to room temperature, water was added. After separation, diethyl ether was used to extract the product. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The concentrated residue was purified by chromatography (0.5-5% EtOAc/hexanes) to afford cyclobutanone **1-111** (720 mg, 83%) as a colorless oil. Cyclobutanone **1-111**: R_f = 0.30 (10% EtOAc/hexanes); IR (neat) 2932, 1772,

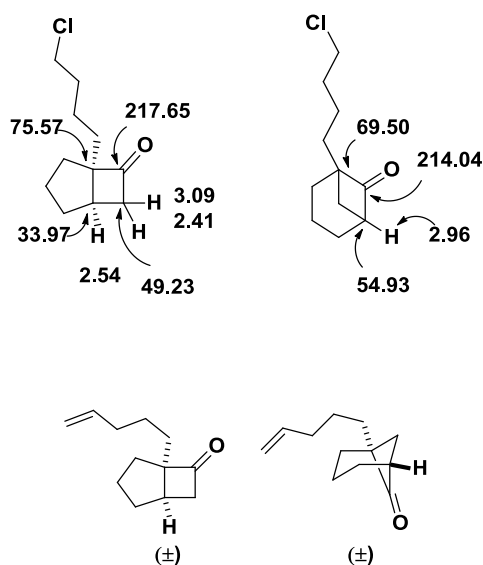
1069 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.25-1.48 (m, 5H), 1.54-1.73 (m, 4H), 1.79-1.83 (m, 2H), 1.98-2.09 (m, 3H), 2.45 (dd, $J = 4.4$ Hz, 18.4 Hz, 1H), 2.55-2.59 (m, 1H), 3.12 (dd, $J = 9.6$ Hz, 18.4 Hz, 1H), 4.94-5.03 (m, 2H), 5.75-5.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.0 (CH_2), 25.1 (CH_2), 29.4 (CH_2), 32.7 (CH_2), 32.9 (CH_2), 33.6 (CH_2), 33.9 (CH), 35.4 (CH_2), 49.3 (CH_2), 75.9 (C), 114.4 (CH_2), 138.8 (CH), 218.3 (C).



(1*R, 5*S**)-5-(4-Chlorobutyl)bicyclo[3.2.0]heptan-6-one (1-101) and (1*R**, 5*R**)-1-(4-chlorobutyl)bicyclo[3.1.1]heptan-6-one (1-163).**

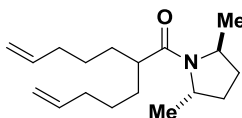
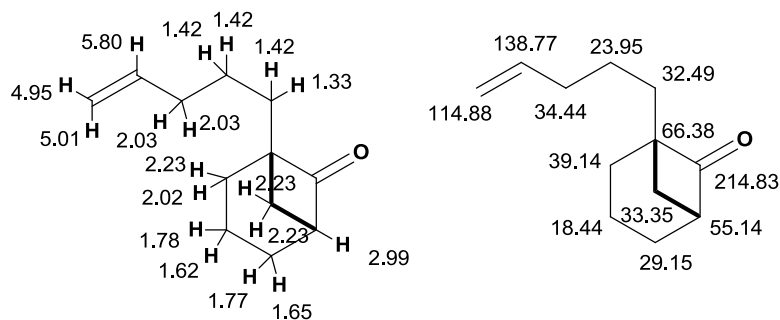
Method I: To a solution of 2-(4-chlorobutyl)hept-6-enoic acid (**1-131**) (1.20 g, 5.50 mmol) and one drop of DMF (2 drops) in benzene (15 mL) at 0 °C under N_2 atmosphere was dropwise added oxalyl chloride (2.40 mL, 27.5 mmol). After 0.5 h at room temperature, the reaction mixture was heated to reflux for 1.5 h. After the reaction was cooled to room temperature, the solvent and excess oxalyl chloride was removed under reduced pressure. Toluene (10 mL) was added and removed again. This procedure was repeated twice. To a refluxing solution of triethylamine (4.63 mL, 33 mmol) in toluene (50 mL) under N_2 atmosphere was added dropwise a solution of the above residue in toluene (15 mL) using syringe pump in 3 h. After the addition, the reaction mixture was allowed to reflux for another 24 h. After the reaction mixture was cooled to room temperature, water was added. After separation, diethyl ether was used to extract the product. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The concentrated residue was purified by chromatography (0.5-5% EtOAc/hexanes) to afford fused cyclobutanone **1-101** (850 mg, 83%) as a colorless oil and a mixture of fused and crossed bicyclobutanone **1-101** and **1-163** (7:1 ratio, 30 mg, 3%) as a colorless oil.

Method II: To a solution of 2-(4-chlorobutyl)-1-(pyrrolidin-1-yl)hept-6-en-1-one **1-131** (865 mg, 3.17 mmol) and 2,6-di-*tert*-butyl-4-methyl pyridine (1.95 g, 9.50 mmol) in anhydrous dichloromethane (50 mL) under N₂ atmosphere at reflux was added dropwise a solution of triflic anhydride (2.23 g, 7.90 mmol) in anhydrous dichloromethane (11 mL) over a period of 10 h using syringe pump. After the addition, the resulting mixture was allowed to reflux for additional 24 h. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. Carbon tetrachloride (25 mL) and water (25 mL) were added and the mixture was heated to reflux for 10 h. The resulting mixture was cooled to room temperature and two phases got separated. The organic phase was dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (1-5% EtOAc/hexanes) to afford a mixture of fused and crossed cyclobutanone **1-101** and **1-163** (15:1 ratio, 150 mg, 39%, 70% brsm) and amide **1-131** (380 mg). Cyclobutanone **1-101**: R_f = 0.30 (20% EtOAc/hexanes); IR (neat) 2945, 1771, 1449 cm⁻¹; HRMS (ESI) m/z calculated for C₁₁H₁₈ClO (M+H)⁺ 201.1046, found: 201.1029; ¹H NMR (400 MHz, CDCl₃) δ 1.32-1.41 (m, 2H), 1.54-1.66 (m, 4H), 1.73-1.83 (m, 6H), 1.97 (dd, J = 6.4 Hz, 12.8 Hz, 1H), 2.41 (dd, J = 4.4 Hz, 18.4 Hz, 1H), 2.53-2.57 (m, 1H), 3.09 (dd, J = 9.6 Hz, 18.4 Hz, 1H), 3.49 (t, J = 6.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 23.0 (CH₂), 24.9 (CH₂), 32.3 (CH₂), 32.6 (CH₂), 32.92 (CH₂), 34.0 (CH), 35.3 (CH₂), 44.7 (CH₂), 49.2 (CH₂), 75.6 (C), 217.7 (C). Ketone **1-163** (diagnostic peaks only): R_f = 0.27 (20% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 2.18-2.23 (m, 2H), 2.95-2.98 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 18.1 (CH₂), 21.8 (CH₂), 28.9 (CH₂), 31.7 (CH₂), 32.90 (CH₂), 33.03 (CH₂), 38.8 (CH₂), 44.8 (CH₂), 54.9 (CH), 65.9 (C), 214.0 (C). The following data were used to assign cyclobutanone **1-101** and **1-163**.



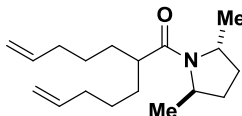
(1*R,5*R**)-5-(Pent-4-enyl)bicyclo[3.2.0]heptan-6-one (1-112)** and **(1*S**,5*R**)-5-(pent-4-enyl)bicyclo[3.1.1]heptan-6-one (1-133)**. According to the procedure described for **(1*R**, 5*S**)-5-(4-chlorobutyl)bicyclo[3.2.0]heptan-6-one 1-101**, **2-(pent-4-en-1-yl)hept-6-enoic acid (1-132)** (600 mg, 3.00 mmol) afforded after chromatography a mixture of fused and crossed bicyclobutanone **1-112** and **1-133** (25:1 ratio, 400 mg, 75%) as a colorless oil. Ketone **1-112**: $R_f = 0.35$ (5% EtOAc/hexanes); chiral GC (column: Astec ChiralDEX™ B-DM; 45-190 °C at 3 °C/min) (±)-**1-112**: $t_R = 31.38$ min and 32.03 min; ^1H NMR (400 MHz, acetone) δ 1.34-1.42 (m, 2H), 1.52-1.71 (m, 4H), 1.79-1.82 (m, 3H), 1.98-2.07 (m, 3H), 2.43 (dd, $J = 4.4$ Hz, 17.2 Hz, 1H), 2.55-2.58 (m, 1H), 3.11 (dd, $J = 8.4$ Hz, 14.4 Hz, 1H), 4.95-5.03 (m, 2H), 5.73-5.82 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 24.9 (CH_2), 25.0 (CH_2), 32.6 (CH_2), 32.7 (CH_2), 34.0 (CH_2), 34.1 (CH_2), 35.3 (CH_2), 75.2 (C), 114.7 (CH_2), 138.4 (CH), 218.2 (C). Ketone **1-133**: $R_f = 0.60$ (10% EtOAc/hexanes); chiral GC (column: Astec ChiralDEX™ B-DM; 45-190 °C at 3 °C/min) (±)-**1-133**: $t_R = 33.34$ min and 33.62 min; IR (neat) 2931, 1771, 1117 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{12}\text{H}_{18}\text{O}+\text{H})^+$ 179.1436, found: 179.1443; ^1H NMR (400 MHz, CDCl_3) δ 1.36-1.47 (m, 3H), 1.48-1.58 (m, 1H), 1.62-1.69 (m,

2H), 1.77-1.87 (m, 2H), 2.00-2.09 (m, 3H), 2.21-2.28 (m, 3H), 2.98-3.03 (m, 1H), 4.95-5.05 (m, 2H), 5.75-5.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.1 (CH_2), 23.8 (CH_2), 28.9 (CH_2), 32.0 (CH_2), 33.1 (CH_2), 34.2 (CH_2), 38.9 (CH_2), 54.9 (CH), 66.2 (C), 114.7 (CH_2), 138.6 (CH), 214.6 (C). The following data were used to assign ketone **1-133**.



1-((2*S*,5*S*)-2,5-Dimethylpyrrolidin-1-yl)-2-(pent-4-enyl)hept-6-en-1-one (1-165).

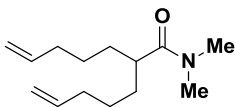
A solution of (*S,S*)-*N*-Boc-2,5-dimethylpyrrolidine (200 mg, 1.00 mmol) in hydrochloric diethyl ether (2.0 M, 10 mL, 20 mmol) was stirred overnight. According to the procedure described for chiral amide (*R,R*)- **1-166**, 2-(pent-4-en-1-yl)hept-6-enoic acid (**1-132**) (200 mg, 1.00 mmol) afforded after chromatography chiral amide **1-165** (160 mg, 75%) as a colorless oil. Amide **1-165**: $[\alpha]_{546}^{25}$ -15.2 (*c* 3.0, dichloromethane). The spectral data matched with the data of **1-166**.



1-((2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-yl)-2-(pent-4-enyl)hept-6-en-1-one (1-166).

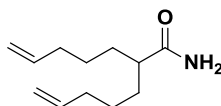
To a stirred solution of 2-(pent-4-enyl)hept-6-enoic acid (**1-132**) (108 mg, 0.550 mmol) and

one drop of DMF in dichloromethane (5 mL) at 0 °C was slowly added oxalyl chloride (0.47 mL, 5.5 mmol). The resulting reaction mixture was allowed to warm to room temperature and was stirred for 5 h. The solvent was removed under reduced pressure. To a stirred solution of (2*R*,5*R*)-2,5-dimethylpyrrolidine (50 mg, 0.50 mmol) and 2.5 M aqueous NaOH (2 mL, 5 mmol) in dichloromethane (6 mL) at 0 °C was slowly added a solution of the above residue in dichloromethane (5 mL). The resulting reaction mixture was allowed naturally to warm to room temperature and was stirred overnight. Saturated aqueous NH₄Cl was used to quench the reaction. The aqueous layer was extracted three times with dichloromethane, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (4-7% EtOAc/hexanes) to afford amide **1-166** (105 mg, 77%) as a colorless oil and amide **1-167** (25 mg, 20%) as a colorless oil. Amide **1-166**: $[\alpha]_{546}^{25} +17.0$ (*c* 3.5, dichloromethane); *R_f* = 0.35 (20% EtOAc/hexanes); IR (neat) 2967, 2930, 1635, 1418 cm⁻¹; HRMS (ESI) *m/z* calculated for (C₁₈H₃₁NO+H)⁺ 278.2484, found: 278.2484; ¹H NMR (400 MHz, CDCl₃) δ 1.15 (d, *J* = 3.2 Hz, 3H), 1.16 (d, *J* = 3.2 Hz, 3H), 1.36-1.43 (m, 5H), 1.45-1.54 (m, 3H), 1.57-1.62 (m, 1H), 1.65-1.70 (m, 1H), 2.01-2.23 (m, 6H), 2.39-2.45 (m, 1H), 4.03 (quintet, *J* = 6.4 Hz, 1H), 4.24 (quintet, *J* = 6.4 Hz, 1H), 4.91-5.00 (m, 4H), 5.72-5.84 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 18.9 (CH₃), 22.5 (CH₃), 26.4 (CH₂), 27.2 (CH₂), 29.0 (CH₂), 30.9 (CH₂), 31.9 (CH₂), 33.3 (CH₂), 33.9 (CH₂), 34.1 (CH₂), 43.4 (CH), 53.0 (CH), 53.2 (CH), 114.4 (CH₂), 114.5 (CH₂), 138.6 (CH), 138.7 (CH), 174.6 (C).

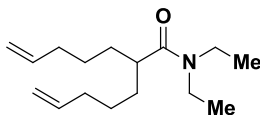


***N,N*-Dimethyl-2-(pent-4-en-1-yl)hept-6-enamide (1-167).** Amide **1-167**: *R_f* = 0.25 (20% EtOAc/hexanes); IR (neat) 2928, 1639, 1398 cm⁻¹; HRMS (ESI) *m/z* calculated for

$C_{14}H_{26}NO$ ($M+H$)⁺ 224.2014, found: 224.2043; ¹H NMR (400 MHz, $CDCl_3$) δ 1.30-1.50 (m, 6H), 1.63-1.71 (m, 2H), 2.01-2.08 (m, 4H), 2.64-2.71 (m, 1H), 2.99 (s, 3H), 3.07 (s, 3H), 4.93-5.02 (m, 4H), 5.74-5.84 (m, 2H); ¹³C NMR (100 MHz, $CDCl_3$) δ 26.9 (CH_2), 32.5 (CH_2), 33.9 (CH_2), 35.7 (CH or CH_3), 37.4 (CH or CH_3), 41.0 (CH or CH_3), 114.6 (CH_2), 138.6 (CH), 176.2 (C).

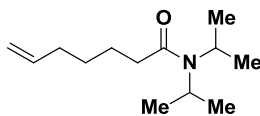


2-(Pent-4-en-1-yl)hept-6-enamide (1-168). According to the procedure described for chiral amide **1-166**, amide **1-168** was obtained as a side product when the reaction was quenched with saturated ammonium chloride. Amide **1-168**: a colorless oil, R_f = 0.30 (100% EtOAc/hexanes); IR (neat) 3374, 2932, 1642, 1460 cm^{-1} ; HRMS (ESI) m/z calculated for $C_{12}H_{22}NO$ ($M+H$)⁺ 196.1701, found: 196.1714; ¹H NMR (400 MHz, $CDCl_3$) δ 1.38-1.50 (m, 6H), 1.58-1.68 (m, 2H), 2.04-2.10 (m, 4H), 2.10-2.15 (m, 1H), 4.95-5.04 (m, 4H), 5.48 (br, 1H), 5.76 (br, 1H), 5.74-5.84 (m, 2H); ¹³C NMR (100 MHz, $CDCl_3$) δ 26.8 (CH_2), 32.4 (CH_2), 33.7 (CH_2), 47.0 (CH), 114.7 (CH_2), 138.4 (CH), 178.4 (C).



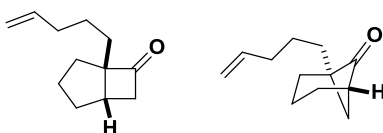
***N,N*-Diethyl-2-(pent-4-en-1-yl)hept-6-enamide (1-169).** To a suspension of 2-(pent-4-en-1-yl)oct-7-enoic acid (50 mg, 0.25 mmol), HOBt (42 mg, 0.30 mmol), DMAP (6 mg, 0.05 mmol), triethylamine (101 mg, 1.00 mmol), and (2*R*,5*R*)-2,5-dimethylpyrrolidine (10 mg, 0.10 mmol) in DMF (3 mL) was added EDCI (60 mg, 0.30 mmol). The resulting mixture was stirred at room temperature overnight. Ethyl acetate and water was added to quench the reaction. After the separation, the aqueous layer was washed with ethyl acetate three times. The combined organic layers were washed with brine and dried over anhydrous

sodium sulfate. The concentrated residue was purified by chromatography (5-20% EtOAc/hexanes) to afford amide **1-169** (28 mg, 44%) as a colorless oil. Amide **1-169**: R_f = 0.20 (20% EtOAc/hexanes); IR (neat) 2931, 1640, 1462 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{16}\text{H}_{30}\text{NO}$ ($\text{M}+\text{H}$)⁺ 252.2327, found: 252.2281; ^1H NMR (400 MHz, CDCl_3) δ 1.13 (t, J = 7.2 Hz, 3H), 1.85 (t, J = 7.2 Hz, 3H), 1.32-1.49 (m, 6H), 1.61-1.70 (m, 2H), 2.02-2.08 (m, 4H), 2.51-2.58 (m, 1H), 3.33-3.43 (m, 4H), 4.93-5.03 (m, 4H), 5.75-5.85 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 13.1 (CH_3), 15.0 (CH_3), 27.0 (CH_2), 32.7 (CH_2), 34.0 (CH_2), 40.4 (CH_2), 41.1 (CH), 41.8 (CH_2), 114.5 (CH_2), 138.7 (CH), 175.2 (C).

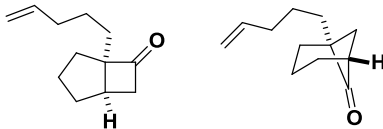


***N,N*-Diisopropylhept-6-enamide (1-170).** To a solution of hept-6-enoic acid (**1-152**) (57 mg, 0.20 mmol) and catalytic amount of DMF (1 drops) in dichloromethane (3 mL) at 0 °C under N_2 atmosphere was dropwise added oxalyl chloride (0.1 mL, 1 mmol). After 0.5 h at room temperature, the solvent and excess oxalyl chloride was removed under reduced pressure. Dichloromethane (10 mL) was added and removed again. The above residue was dissolved in dichloromethane (5 mL) under N_2 atmosphere and cooled to 0 °C. Diisopropylethylamine (128 mg, 1.00 mmol) and (2*R*,5*R*)-2,5-dimethylpyrrolidine (10 mg, 0.10 mmol) was added slowly. The reaction mixture was stirred overnight. Water was used to quench the reaction. After separation, dichloromethane was used to extract the product. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The concentrated residue was purified by chromatography (5-20% EtOAc/hexanes) to afford amide **1-170** (62 mg, 66%) as a colorless oil. Amide **1-170**: R_f = 0.25 (20% EtOAc/hexanes); IR (neat) 2966, 1645, 1441 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{25}\text{NONa}$ ($\text{M}+\text{Na}$)⁺ 234.1834, found: 234.1834; ^1H NMR (400 MHz, CDCl_3) δ 1.19 (d, J

= 6.4 Hz, 3H), 1.37 (d, J = 6.4 Hz, 3H), 1.37-1.47 (m, 2H), 1.59-1.67 (m, 2H), 2.05-2.11 (m, 2H), 2.25-2.29 (m, 2H), 3.47 (br, 1H), 3.92-3.99 (m, 1H), 4.92-5.03 (m, 1H), 5.75-5.85 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.7 (CH_3), 21.0 (CH_3), 24.9 (CH_2), 28.7 (CH_2), 33.6 (CH_2), 35.2 (CH_2), 45.5 (CH), 48.2 (CH), 114.4 (CH_2), 138.7 (CH), 171.8 (C).



(1S,5S)-5-(Pent-4-enyl)bicyclo[3.2.0]heptan-6-one ((S)-1-112) and **(1R,5S)-5-(pent-4-enyl) bicyclo[3.1.1]heptan-6-one ((S)-1-133)**. According to the procedure described for **(R)-1-112**, amide **1-166** afforded after chromatography **(S)-1-112** (61%). Iminium ion **(S)-1-171** and **(S)-1-172**: $[\alpha]_{546}^{25} +79.0$ (c 1.2, dichloromethane); Ketone **(S)-1-112**: $[\alpha]_{546}^{25} +73.0$ (c 0.12, dichloromethane).

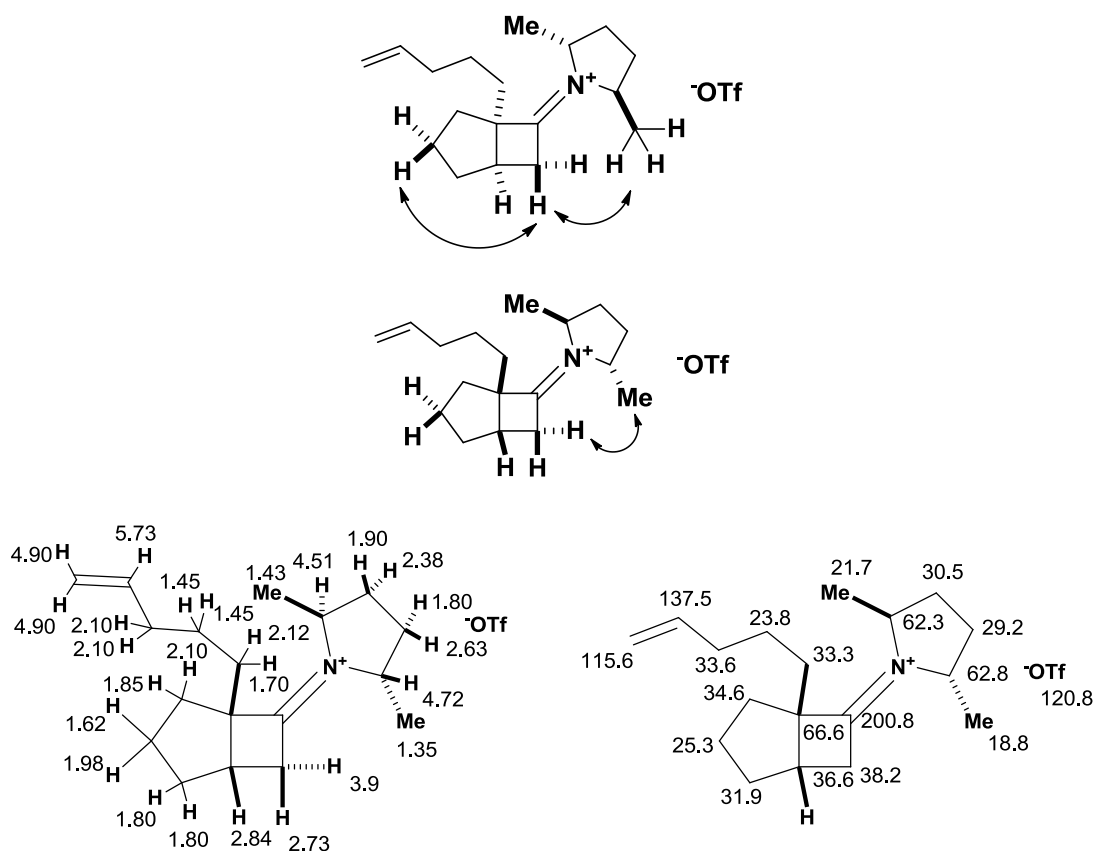


(1R,5R)-5-(Pent-4-enyl)bicyclo[3.2.0]heptan-6-one ((R)-1-112) and **(1S,5R)-5-(pent-4-enyl) bicyclo[3.1.1]heptan-6-one ((R)-1-133)**. *One-pot procedure*: To a refluxing solution of amide **1-166** (87 mg, 0.31 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (81 mg, 0.39 mmol) in 1,2-dichloroethane (5 mL) was added a solution of triflic anhydride (97 mg, 0.35 mmol) in 1,2-dichloroethane (2 mL) over 12 h using a syringe pump. The solution was allowed to reflux for another 5 h, after which the reaction was cooled to room temperature and concentrated. To the residue in a mixed solvent of acetone (4 mL) and water (4 mL) was added potassium carbonate (217 mg, 1.57 mmol). The resulting mixture was heated to reflux for 3 h. After the reaction was cooled to room temperature, 1 M HCl was used to adjust the pH to 2-3. The aqueous layer was extracted three times with diethyl ether, washed with brine,

dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0.1% EtOAc/hexanes) to afford ketone **(R)-1-112** (34 mg, 61%) as a colorless oil and ketone **(R)-1-133** (5 mg, 9%) as a colorless oil. Ketone **(R)-1-112**: $[\alpha]_{546}^{25}$ -100.0 (*c* 1.35, dichloromethane); t_R = 32.03 min (chiral GC column: Astec ChiralDEX™ B-DM; 45-190 °C at 3 °C/min); R_f = 0.65 (10% EtOAc/hexanes); spectral data matched with reported data.^{S13} Ketone **(R)-1-133**: t_R = 33.62 (chiral GC column: Astec ChiralDEX™ B-DM; 45-190 °C at 3 °C/min).

Two-pot procedure: To a refluxing solution of amide **1-166** (43 mg, 0.155 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (40 mg, 0.194 mmol) in 1,2-dichloroethane (5 mL) was added a solution of triflic anhydride (48 mg, 0.17 mmol) in 1,2-dichloroethane (2 mL) over 12 h using syringe pump. The solution was allowed to reflux for another 5 h, after which the reaction was cooled down to room temperature and concentrated. The resulting residue was purified by silica gel chromatography (0.5%-4% MeOH/DCM) to afford a mixture of iminium ion **(R)-1-171** and **(R)-1-172** as a colorless oil (55 mg, 87%, 7:1 ratio). Iminium ion **(R)-1-171** and **(R)-1-172**: $[\alpha]_{546}^{25}$ -115.0 (*c* 1.05, DCM); HRMS (ESI) *m/z* calculated for (M-OTf)⁺ (C₁₈H₃₀N⁺) 260.2378, found: 260.2351. IR (neat): 2941, 1684, 1263, 1152, 1030 cm⁻¹. Iminium ion **(R)-1-171**: ¹H NMR (400 MHz, CDCl₃) δ 1.39 (d, *J* = 6.8 Hz, 3H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.38-1.52 (m, 2H), 1.58-1.68 (m, 1H), 1.69-1.75 (m, 1H), 1.76-1.85 (m, 4H), 1.92 (dd, *J* = 6.4 Hz, 12.8 Hz, 1H), 1.98-2.04 (m, 1H), 2.06-2.18 (m, 3H), 2.40 (septet, *J* = 6.8 Hz, 1H), 2.61 (septet, *J* = 6.8 Hz, 1H), 2.74 (dd, *J* = 4.0 Hz, 20.4 Hz, 1H), 2.90 (quintet, *J* = 4.8 Hz, 1H), 3.91 (dd, *J* = 6.0 Hz, 20.4 Hz, 1H), 4.50 (quintet, *J* = 6.8 Hz, 1H), 4.84 (quintet, *J* = 6.8 Hz, 1H), 4.98-5.06 (m, 2H), 5.72-5.83 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 18.9 (CH₃), 21.8 (CH₃), 23.8 (CH₂), 25.3 (CH₂), 29.3 (CH₂), 30.6 (CH₂), 31.9 (CH₂), 33.3

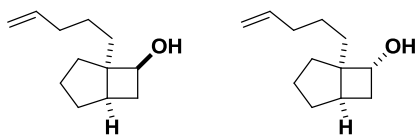
(CH₂), 33.6 (CH₂), 34.7 (CH₂), 36.7 (CH), 38.2 (CH₂), 62.3 (CH), 62.8 (CH), 66.6 (C), 115.7 (CH₂), 120.9 (q, $J = 317$ Hz, CF₃), 137.5 (CH), 200.3 (C); ¹⁹F NMR (376.5 MHz, CDCl₃) δ -78.24. Iminium ion (**R**)-**1-172** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 1.41 (d, $J = 6.8$ Hz, 3H), 1.51 (d, $J = 6.8$ Hz, 3H), 3.68 (t, $J = 6.8$ Hz, 1H), 4.58 (quintet, $J = 6.8$ Hz, 1H), 4.92 (quintet, $J = 6.8$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 19.1 (CH₂), 20.9 (CH₂), 22.4 (CH₂), 23.3 (CH₂), 29.6 (CH₂), 33.5 (CH₂), 33.7 (CH₂), 35.1 (CH₂), 36.8 (CH₂), 39.8 (CH₂), 48.1 (CH₂), 60.9 (CH₂), 62.3 (CH₂), 63.6 (CH₂), 115.5 (CH₂), 137.6 (CH), 199.0 (C). The following data and NOE correlations were used to assign Iminium ion (**R**)-**1-171** and (**S**)-**1-171**.



To a mixture of iminium ions (**R**)-**1-171** and (**R**)-**1-172** (55 mg, 0.135 mmol) in a mixed solvent of acetone (3 mL) and water (3 mL) was added potassium carbonate (93 mg,

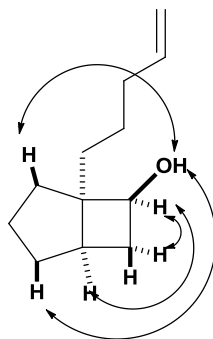
0.68 mmol). The resulting mixture was heated to reflux for 3 h. After the reaction was cooled down to room temperature, 1 M HCl was used to adjust to pH = 2~3. Diethyl ether was used to extract the product. The aqueous layer was extracted three times with diethyl ether, washed with brine, dried over Na₂SO₄, filtered and concentrated. The resulting residue was purified by silica gel chromatography (0.1% EtOAC/hexanes) to afford ketone **(R)-1-112** (17 mg, 71%) as a colorless oil and ketone **(R)-1-133** (2.5 mg, 10%) as a colorless oil.

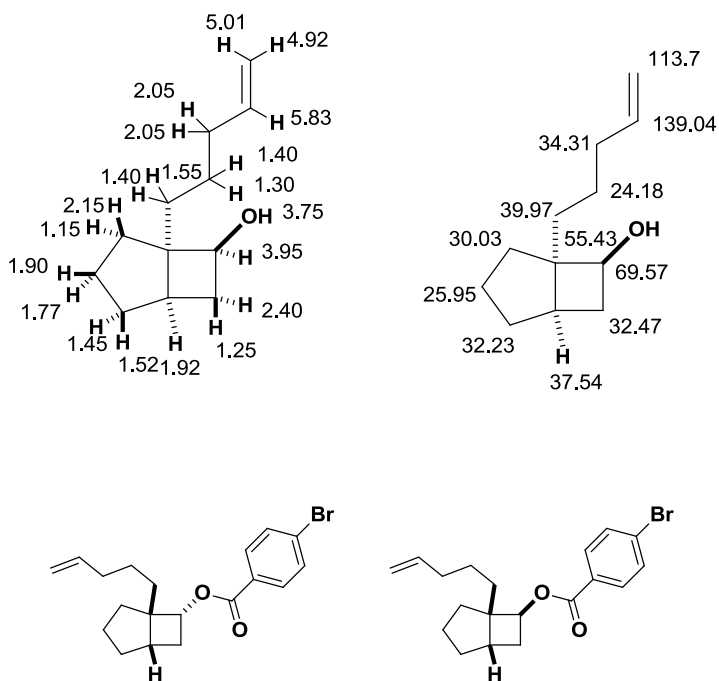
Recovery of (2R,5R)-2,5-dimethylpyrrolidine A stirred aqueous solution (~10 mL) from the above procedure, which contains (2R,5R)-2,5-dimethylpyrrolidine (~ 0.97 mmol), was adjusted to pH ~ 13-14 using 2.5 M aqueous NaOH, followed by the addition of DCM (10 mL). The resulting mixture was cooled to 0 °C and a solution of 2-(pent-4-enyl)hept-6-enoyl chloride (1.1 mmol) in DCM (5 mL) was added slowly. The resulting reaction mixture was allowed naturally to rise to room temperature and was stirred overnight. Saturated aqueous NH₄Cl was used to quench the reaction. The aqueous layer was extracted 3× with DCM, washed with brine, dried over Na₂SO₄, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (4%-7% EtOAC/hexanes) to afford **1-166** (176 mg, 65%, recovery rate: 85%) as a colorless oil.



(1R*,5R*,6S*)-5-(Pent-4-en-1-yl)bicyclo[3.2.0]heptan-6-ol (1-173) and **(1R*,5R*,6R*)-5-(pent-4-en-1-yl)bicyclo[3.2.0]heptan-6-ol (1-174)**. To a solution of cyclobutanone **1-112** (166 mg, 0.930 mmol) in methanol (12 mL) at 0 °C under N₂ atmosphere was added slowly sodium borohydride (106 mg, 2.80 mmol). After the reaction mixture was stirred for 3 h, aqueous ammonium chloride was used to quench the reaction. Methanol was removed under reduced pressure. Diethyl ether and water were added and after

the separation, the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine and dried over sodium sulfate. The concentration afforded a mixture of alcohols **1-173** and **1-174** (10:1 ratio, 150 mg, 90%) as a colorless oil, which was used directly in the next step. Alcohols **1-173** and **1-174** (10:1 ratio): IR (neat) 3336, 2930, 1074 cm^{-1} ; Alcohol **1-173**: ^1H NMR (400 MHz, acetone) δ 1.13 (td, $J = 11.6, 7.4$ Hz, 1H), 1.21-1.36 (m, 2H), 1.37-1.47 (m, 3H), 1.48-1.58 (m, 2H), 1.70-1.80 (m, 1H), 1.88-1.99 (m, 2H), 2.00-2.13 (m, 3H), 2.36 (dt, $J = 12.6, 8.8$ Hz, 1H), 3.75 (d, $J = 5.4$ Hz, 1H), 3.95 (dt, $J = 8.8, 6.1$ Hz, 1H), 4.88-4.96 (m, 1H), 4.96-5.06 (m, 1H), 5.82 (ddt, $J = 17.0, 10.2, 6.7$ Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 24.2 (CH_2), 26.0 (CH_2), 30.0 (CH_2), 32.2 (CH_2), 32.5 (CH_2), 34.3 (CH_2), 37.5 (CH), 40.0 (CH_2), 55.4 (C), 69.6 (CH), 113.8 (CH_2), 139.0 (CH). Alcohol **1-174** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.85-3.92 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 24.4 (CH_2), 25.5 (CH_2), 31.9 (CH_2), 32.2 (CH_2), 33.8 (CH_2), 34.7 (CH_2), 36.3 (CH_2), 37.3 (CH), 54.5 (C), 71.2 (CH), 113.6 (CH_2), 139.2 (CH). The following data and NOE correlations were used to assign alcohol **1-173**.





(1*S*,5*S*,6*R*)-5-(Pent-4-en-1-yl)bicyclo[3.2.0]heptan-6-yl 4-bromobenzoate (1-175)

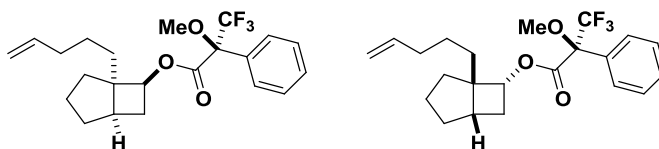
and **(1*S*,5*S*,6*S*)-5-(pent-4-en-1-yl)bicyclo[3.2.0]heptan-6-yl 4-bromobenzoate (1-176).**

According to the procedure for the preparation of alcohols **1-173** and **1-174**, (*S*)-**1-112** (28 mg, 0.16 mmol) afforded a mixture of alcohols, which was used directly in the next step without further purification. According to the procedure described for lactam **1-207**, the above residue and 4-bromobenzoyl chloride (110 mg, 0.500 mmol) afforded after chromatography (0.1% EtOAc/hexanes) a mixture of ester **1-175** and **1-176** (47 mg, 82%) as

a powder. Ester **1-175** and **1-176** (10:1 ratio): $[\alpha]_{546}^{25} -18.7$ (*c* 2.45, dichloromethane); $R_f =$

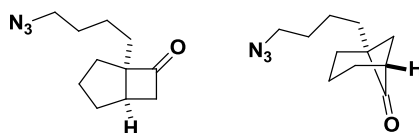
0.85 (10% EtOAc/hexanes); IR (neat) 2933, 1717 cm^{-1} ; Ester **1-175**: ^1H NMR (400 MHz, CDCl_3) δ 1.25-1.49 (m, 4H), 1.51-1.72 (m, 4H), 1.83-1.92 (m, 1H), 1.94-2.03 (m, 2H), 2.07 (q, $J = 7.1$ Hz, 2H), 2.19 (q, $J = 6.4$ Hz, 1H), 2.63 (dt, $J = 13.5, 8.9$ Hz, 1H), 4.93-5.08 (m, 3H), 5.82 (ddt, $J = 16.9, 10.1, 6.7$ Hz, 1H), 7.60 (d, $J = 8.6$ Hz, 2H), 7.91 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.3 (CH_2), 26.1 (CH_2), 30.1 (CH_2), 31.7 (CH_2), 32.9 (CH_2),

34.3 (CH₂), 38.2 (CH), 38.8 (CH₂), 54.8 (C), 73.1 (CH), 114.5 (CH₂), 127.9 (C), 129.5 (C), 131.0 (CH), 131.7 (CH), 138.9 (CH), 165.1 (C). Ester **1-176** (diagnostic peaks only): ¹³C NMR (100 MHz, CDCl₃) δ 24.5 (CH₂), 25.9 (CH₂), 31.3 (CH₂), 32.0 (CH₂), 32.2 (CH₂), 34.6 (CH₂), 36.2 (CH₂), 38.0 (CH), 52.3 (C), 74.8 (CH), 114.5 (CH₂), 131.1 (CH), 131.1 (CH), 131.7 (CH), 138.9 (CH).

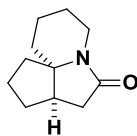


(S)-(1R,5R,6S)-5-(Pent-4-en-1-yl)bicyclo[3.2.0]heptan-6-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1-177) and **(S)-(1S,5S,6R)-5-(pent-4-en-1-yl)bicyclo[3.2.0]heptan-6-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1-178)**. To a suspension of Mosher's acid (117 mg, 0.500 mmol) and two drops of DMF in hexane (10 mL) at room temperature under N₂ atmosphere was added slowly oxalyl chloride (0.43 mL, 5 mmol). After the resulting mixture was stirred for 2 h, the solid residue was filtrated and the filtrate concentrated. To the resulting residue and DMAP (122 mg, 1.00 mmol) was added a solution of alcohol **1-173** and **1-174** (10:1 ratio, 40 mg, 0.22 mmol) in dichloromethane (3 mL) at room temperature. After stirred overnight, the resulting mixture was concentrated. The concentrated residue was purified by chromatography (0.25% EtOAc/hexanes) to afford a mixture of esters **1-177** and **1-178** (1:1 ratio, 84 mg, 96%) as a powder. Esters **1-177** and **1-178** (1:1 ratio): *R_f* = 0.45 (5% EtOAc/hexanes); IR (neat) 2948, 1747, 1169 cm⁻¹; HRMS (ESI) *m/z* calculated for C₄₄H₅₄F₆O₆Na (2M+Na)⁺ 815.3722, found: 815.3718; ¹H NMR (400 MHz, acetone) δ 1.15-1.34 (m, 3H), 1.34-1.64 (m, 11H), 1.64-1.88 (m, 7H), 1.96 (ddd, *J* = 13.4, 5.5, 4.0 Hz, 1H), 2.01-2.12 (m, 4H), 2.17 (q, *J* = 6.5 Hz, 2H), 2.62 (dtd, *J* = 13.4, 8.8, 2.5 Hz, 2H), 3.57 (q, *J* = 1.0 Hz, 3H), 3.58 (q, *J* = 1.0 Hz, 3H), 4.91-5.15 (m, 6H), 5.80-5.88 (m, 2H),

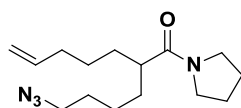
7.46-7.53 (m, 6H), 7.53-7.60 (m, 4H); ^{13}C NMR (100 MHz, acetone) δ 24.0 (CH_2), 24.2 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 31.3 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 33.97 (CH_2), 34.00 (CH_2), 38.3 (CH), 38.5 (CH), 38.8 (CH_2), 38.9 (CH_2), 54.3 (CH), 54.84 (C), 54.87 (C), 54.89 (C), 54.90 (C), 54.92 (C), 74.2 (CH), 74.5 (CH), 113.97 (CH_2), 114.01 (CH_2), 123.61 (q, $J = 286$ Hz, C), 123.64 (q, $J = 286$ Hz, C), 127.29 (CH), 127.31 (CH), 127.37 (CH), 127.38 (CH), 128.37 (CH), 128.39 (CH), 129.62 (CH), 129.64 (CH), 132.4 (C), 132.5 (C), 138.7 (CH), 165.2 (C), 165.2 (C).



(1*R, 5*S**)-5-(4-Azidobutyl)bicyclo[3.2.0]heptan-6-one (1-100)** and **(1*R**, 5*R**)-1-(4-azidobutyl)bicyclo[3.1.1]heptan-6-one**. The suspension of a mixture of fused and crossed cyclobutanone **1-101** and **1-163** (~20:1 ratio, 243 mg, 1.20 mmol) and sodium azide (390 mg, 6.00 mmol) in DMF (3 mL) under N_2 atmosphere was heated to 80 $^\circ\text{C}$ for 4 h. After the reaction mixture was cooled to room temperature, diethyl ether and water were added. After the separation, the aqueous layer was extracted with diethyl ether three times. The combined layers were washed with water, brine, and dried over anhydrous sodium sulfate. The concentrated residue was directly used in the next step without further purification. Azide **1-100**: ^1H NMR (400 MHz, CDCl_3) δ 1.29-1.46 (m, 3H), 1.50-1.70 (m, 5H), 1.75-1.89 (m, 3H), 2.03 (dd, $J = 12.7, 6.2$ Hz, 1H), 2.46 (dd, $J = 18.5, 4.6$ Hz, 1H), 2.54-2.61 (m, 1H), 3.13 (dd, $J = 18.4, 9.5$ Hz, 1H), 3.29 (t, $J = 6.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.9, 25.0, 29.3, 32.68, 32.70, 34.0, 35.3, 49.3, 51.2, 75.6, 217.8. Crossed azide (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 2.19-2.28 (m, 3H), 2.98-3.04 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.1, 21.7, 28.9, 32.0, 33.1, 38.9, 51.3, 55.0, 65.9, 214.2.

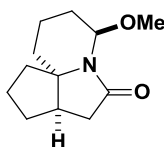


Octahydrocyclopenta[1]indolizin-6(7H)-one (1-99). To a solution of the above residue in dichloromethane (10 mL) at 0 °C under N₂ atmosphere was added slowly titanium tetrachloride (1 M in DCM, 3.6 mL, 3.6 mmol). After the reaction mixture stirred overnight, saturated aqueous sodium bicarbonate was used to quench the reaction. After the separation, the aqueous layer was extracted with DCM three times. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (50-200% EtOAc/hexanes) to afford lactam **1-99** (200 mg, 93%) as a colorless oil. Lactam **1-99**: R_f = 0.35 (100% EtOAc/hexanes); IR (neat) 2936, 1682, 1417 cm⁻¹; HRMS (ESI) m/z calculated for C₁₁H₁₈NO (M+H)⁺ 180.1388, found: 180.1391; ¹H NMR (400 MHz, CDCl₃) δ 1.20-1.60 (m, 9H), 1.64-1.68 (m, 1H), 1.72-1.84 (m, 2H), 1.94-2.00 (m, 1H), 2.11-2.18 (m, 1H), 2.52-2.60 (m, 2H), 3.97 (dd, J = 2.8 Hz, 13.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.7 (CH₂), 24.5 (CH₂), 25.0 (CH₂), 33.9 (CH₂), 34.9 (CH₂), 37.5 (CH₂), 37.8 (CH₂), 37.8 (CH₂), 41.8 (CH), 71.3 (C), 172.3 (C).



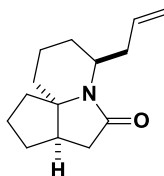
2-(4-Azidobutyl)-1-(pyrrolidin-1-yl)hept-6-en-1-one (1-185). A suspension of chloride **1-131** (733 mg, 2.68 mmol) and sodium azide (873 mg, 13.4 mmol) in DMF (10 mL) was heated to 80 °C for 2 h. Diethyl ether and water were added to quench the reaction. After separation, the aqueous layer was extracted with diethyl ether three times. The combined organic layers were washed with brine, and dried over anhydrous sodium sulfate. The concentration afforded azide **1-185** (811 mg, 104%) as a colorless oil, which was used directly in the next step. Azide **1-185**: IR (neat) 2935, 2095, 1638, 1433 cm⁻¹; HRMS (ESI)

m/z calculated for $C_{30}H_{53}N_6O_2$ ($2M-N_2+H$)⁺ 529.4230, found: 529.4257; ¹H NMR (400 MHz, CDCl₃) δ 1.27-1.48 (m, 6H), 1.53-1.60 (m, 2H), 1.61-1.72 (m, 2H), 1.82-1.87 (m, 2H), 1.92-1.97 (m, 2H), 1.99-2.06 (m, 2H), 2.46 (tt, J = 9.1, 5.0 Hz, 1H), 3.17-3.31 (m, 2H), 3.47 (q, J = 7.1 Hz, 4H), 4.90-4.95 (m, 1H), 4.98 (dq, J = 17.2, 1.6 Hz, 1H), 5.77 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.4, 24.9, 26.2, 26.9, 29.1, 32.4, 32.5, 33.9, 43.8, 45.6, 46.7, 51.3, 114.6, 138.6, 174.4.

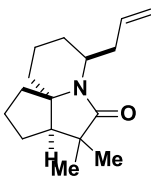


(4*R,7*aR**,10*aS**)-4-Methoxyoctahydrocyclopenta[*i*]indolizin-6(7*H*)-one (1-187).**

To a three-necked round-bottom flask equipped with graphite anode, graphite cathode, and stirring bar, was added under N₂ atmosphere a solution of octahydrocyclopenta[*i*]indolizin-6(7*H*)-one (**1-99**) and tetraethylammonium tosylate (603 mg, 2.00 mmol) in anhydrous methanol (20 mL). Our home-made apparatus was used to charge the potential. The resulting reaction mixture was stirred for 48 h. The solvent was removed under reduced pressure. Diethyl ether was added to the residue and some white solid formed. After the filtration, the filtrate was concentrated to afford lactam **1-187**, which was used in the next step without further purification. Pure sample was obtained after column chromatography. Lactam **1-187**: a colorless oil, R_f = 0.55 (EtOAc); IR (neat) 2939, 1689, 1398 cm⁻¹; HRMS (ESI) m/z calculated for $C_{12}H_{19}NO_2Na$ ($M+Na$)⁺ 232.1313, found: 232.1290; ¹H NMR (400 MHz, CDCl₃) δ 1.42-1.75 (m, 8H), 1.81-1.93 (m, 3H), 2.11-2.26 (m, 3H), 2.69 (dd, J = 2.8 Hz, 8.6 Hz, 1H), 3.26 (s, 3H), 5.25 (d, J = 4.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.1 (CH₂), 25.1 (CH₂), 30.1 (CH₂), 33.7 (CH₂), 37.8 (CH₂), 38.0 (CH₂), 38.1 (CH₂), 42.4 (CH), 55.2 (CH₃), 70.8 (C), 79.7 (CH), 175.2 (C).

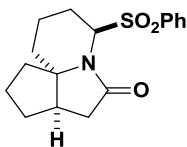


(4*S,7*aR**,10*aS**)-4-Allyloctahydrocyclopenta[*i*]indolizin-6(7*H*)-one (1-189).** To a solution of the above residue and allyl trimethylsilane (103 mg, 0.900 mmol) in anhydrous dichloromethane (10 mL) at 0 °C under N₂ atmosphere was added dropwise titanium tetrachloride (1 M in DCM, 0.3 mL, 0.3 mmol). The resulting reaction mixture was stirring overnight at room temperature. Saturated aqueous sodium bicarbonate was used to quench the reaction. After separation, the aqueous layer was extracted with DCM three times. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (20-200% EtOAc/hexanes) to afford lactam **1-189** (13 mg, 56%) as a colorless oil and eliminated lactam **1-191** (5 mg, 27%) as a colorless oil. (No eliminated product was observed when the reaction was carried out at -78 °C). Lactam **1-189**: *R*_f = 0.35 (100% EtOAc/hexanes); IR (neat) 2936, 1678, 1404 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₄H₂₂NO (M+H)⁺ 220.1701, found: 220.1694; ¹H NMR (400 MHz, CDCl₃) δ 1.32-1.42 (m, 2H), 1.44-1.69 (m, 3H), 1.69-1.85 (m, 6H), 1.92-2.02 (m, 1H), 2.11-2.18 (m, 1H), 2.18-2.25 (m, 1H), 2.28-2.47 (m, 2H), 2.61-2.70 (m, 1H), 4.41 (q, *J* = 7.4 Hz, 1H), 5.04-5.06 (m, 1H), 5.06-5.12 (m, 1H), 5.80 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.3 (CH₂), 25.6 (CH₂), 27.2 (CH₂), 33.4 (CH₂), 37.3 (CH₂), 37.9 (CH₂), 38.0 (CH₂), 38.3 (CH₂), 43.5 (CH), 47.9 (CH), 70.6 (C), 117.0 (CH₂), 135.9 (CH), 173.5 (C).



(4*S*,7*aR*,10*aS*)-4-Allyl-7,7-dimethyloctahydrocyclopenta[*i*]indolizin-6(7*H*)-one.

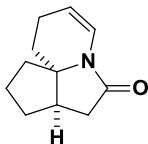
To a solution of lactam **1-189** (16 mg, 0.073 mmol) in anhydrous THF (5 mL) at -78 °C under N₂ atmosphere was added dropwise freshly-prepared LDA (1 M in THF, 0.22 mL, 0.22 mmol). After the resulting mixture was stirred for 0.5 h at -78 °C, methyl iodide (142 mg, 1 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride was added to quench the reaction. After the separation, the aqueous layer was extracted with ethyl acetate three times and the combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (2-20% EtOAc/hexanes) to afford the title lactam (7 mg, 39%) as a colorless oil. Lactam: *R_f* = 0.25 (20% EtOAc/hexanes); IR (neat) 2932, 1677 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₆H₂₆NO (M+H)⁺ 248.2014, found: 248.1988; ¹H NMR (400 MHz, CDCl₃) δ 1.10 (s, 3H), 1.21 (s, 3H), 1.32-1.41 (m, 1H), 1.46-1.85 (m, 10H), 1.87-1.93 (m, 1H), 1.93-2.00 (m, 1H), 2.28-2.46 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 1H), 5.01-5.11 (m, 2H), 5.79 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.6, 22.1, 25.9, 27.0, 27.4, 30.0, 37.3, 38.4, 38.4, 42.0, 47.9, 55.9, 67.9, 116.8, 136.0, 178.9.



(4*R,7*aR**,10*aS**)-4-(Phenylsulfonyl)octahydrocyclopenta[*i*]indolizin-6(7*H*)-one**

(1-190). According to the procedure described for the preparation of lactam **1-187**, lactam **1-99** (179 mg, 1.00 mmol) afforded after chromatography lactam **1-187** (76 mg, 36%) and **1-**

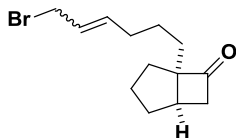
188 (106 mg). To a white suspension of **1-188** (100 mg), benzenesulfinic acid sodium salt (246 mg, 1.5 mmol), and magnesium sulfate (180 mg, 1.50 mmol) in dichloromethane (5 mL) at room temperature under N₂ atmosphere was added slowly TFA (171 mg, 1.50 mmol). The reaction mixture was stirred overnight. Water was added to quench the reaction, and the aqueous layer was washed with dichloromethane three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (2-20% EtOAc/hexanes) to afford lactam **1-190** (45 mg, 30%) as a colorless oil and lactam **1-191** (17 mg, 20%) as a colorless oil. Lactam **1-190**: R_f = 0.35 (100% EtOAc/hexanes); IR (neat) 2945, 1664, 1145 cm⁻¹; HRMS (ESI) m/z calculated for C₁₇H₂₁NO₃SNa (M+Na)⁺ 342.1140, found: 342.1133; ¹H NMR (400 MHz, CDCl₃) δ 1.40-1.52 (m, 2H), 1.65-1.82 (m, 5H), 1.85-1.93 (m, 2H), 2.07 (dd, J = 6.4 Hz, 18.0 Hz, 1H), 2.23-2.37 (m, 2H), 2.42-2.62 (m, 3H), 5.42 (d, J = 7.6 Hz, 1H), 7.28-7.59 (m, 2H), 7.64-7.68 (m, 1H), 7.97-7.99 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 17.8 (CH₂), 22.5 (CH₂), 24.9 (CH₂), 33.0 (CH₂), 37.2 (CH₂), 37.5 (CH₂), 37.6 (CH₂), 43.7 (CH), 68.8 (CH), 70.7 (C), 129.0 (CH), 129.1 (CH), 133.9 (CH), 137.9 (C), 175.1 (C).



(7aR*,10aS*)-1,2,7a,8,9,10-hexahydrocyclopenta[i]indolizin-6(7H)-one (1-191).

Lactam **1-191**: R_f = 0.45 (100% EtOAc/hexanes); IR (neat) 2951, 1745, 1694 cm⁻¹; HRMS (ESI) m/z calculated for C₁₁H₁₆NO (M+H)⁺ 178.1232, found: 178.1222; ¹H NMR (400 MHz, CDCl₃) δ 1.35-1.43 (m, 1H), 1.64-1.86 (m, 7H), 2.16-2.24 (m, 3H), 2.41-2.47 (m, 1H), 2.73 (dd, J = 10.8 Hz, 18.0 Hz, 1H), 5.14-5.17 (m, 1H), 6.76 (dt, J = 2.0 Hz, 6.0 Hz, 1H); ¹³C

NMR (100 MHz, CDCl₃) δ 21.0 (CH₂), 23.8 (CH₂), 32.8 (CH₂), 33.3 (CH₂), 37.1 (CH₂), 37.9 (CH₂), 41.7 (CH), 69.9 (C), 110.1 (CH), 121.4 (CH), 171.7 (C).

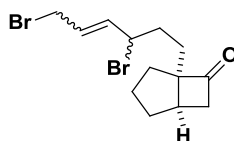


(1*R*,5*S*)-5-(6-Bromohex-4-enyl)bicyclo[3.2.0]heptan-6-one (1-192).

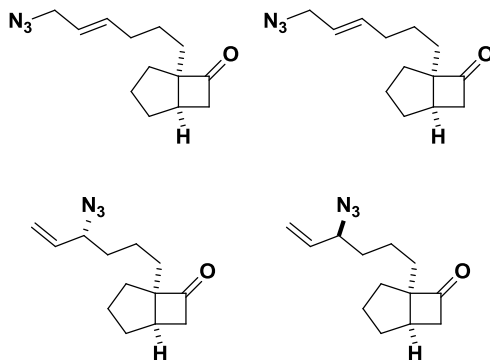
Method I: To a stirred solution of Hoveyda-Grubbs 2nd generation catalyst (32 mg, 0.050 mmol, 5 mol%) in dichloromethane (2 mL) under N₂ atmosphere at room temperature was slowly added a solution of ketone (**R**)-**1-112** (154 mg, 0.860 mmol) and allyl bromide (0.25 mL, 3.0 mmol) in dichloromethane (2 mL). The reaction mixture was stirred overnight, then concentrated and the residue was purified by silica gel chromatography (0.05%-0.5% EtOAc/hexanes) to afford bromide (**R**)-**1-192** as an oil (173 mg, 74% (or 82% brsm), *E/Z* 8:1) and ketone (**R**)-**1-112** (15 mg). Bromide (**R**)-**1-192**: $[\alpha]_{546}^{25}$ -68.0 (*c* 4.7, dichloromethane); *R_f* = 0.55 (10% EtOAc/hexanes); IR (neat) 2938, 1766, 1205 cm⁻¹. *E* isomer: ¹H NMR (400 MHz, CDCl₃) δ 1.34-1.44 (m, 2H), 1.53-1.71 (m, 4H), 1.78-1.85 (m, 3H), 1.98-2.09 (m, 3H), 2.45 (dd, *J* = 4.4 Hz, 18.4 Hz, 1H), 2.55-2.59 (m, 1H), 3.11 (dd, *J* = 9.6 Hz, 18.4 Hz, 1H), 3.95 (d, *J* = 6.4 Hz, 2H), 5.67-5.75 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 24.9 (CH₂), 25.0 (CH₂), 32.4 (CH₂), 32.68 (CH₂), 32.77 (CH₂), 33.4 (CH₂), 34.0 (CH), 35.4 (CH₂), 49.3 (CH₂), 75.7 (C), 126.8 (CH), 135.8 (CH), 217.96 (C). *Z* isomer (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 4.01 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 25.2 (CH₂), 27.17 (CH₂), 27.26 (CH₂), 32.8 (CH₂), 75.6 (C), 125.7 (CH), 135.2 (CH), 217.89 (C).

Method II: To a solution of cyclobutanone **1-111** (500 mg, 2.60 mmol) and NBS (510 mg, 2.86 mmol) in chlorobenzene (26 mL) at refluxing temperature under N₂ atmosphere was added catalytic amount of BPO. The heating was continued for 7 h. After the

resulting mixture was cooled to room temperature, the solvent was removed under reduced temperature. The concentrated residue was purified by chromatography (1.5% EtOAc/hexanes) to afford bromide **1-192** (320 mg, 45%, 66% brsm *E/Z* 10:1), dibromide **1-192a** (76 mg, 8%, 12% brsm) and cyclobutanone **1-111** (154 mg).

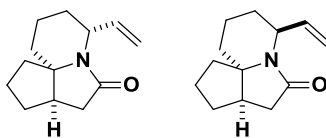


(1*R,5*S**)-5-(3,6-Dibromohex-4-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-192a).** R_f = 0.50 (10% EtOAc/hexanes); IR (neat) 2947, 1768, 1204 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.33-1.43 (m, 1H), 1.63-1.74 (m, 2H), 1.74-1.94 (m, 5H), 2.00-2.12 (m, 2H), 2.47 (dd, J = 18.5, 4.6 Hz, 1H), 2.51-2.61 (m, 1H), 3.15 (ddd, J = 18.5, 9.4, 4.2 Hz, 1H), 3.94 (d, J = 5.7 Hz, 2H), 4.46 (dd, J = 8.5, 5.4 Hz, 1H), 5.86-5.92 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.96, 25.00, 30.98, 30.99, 31.2, 31.4, 32.60, 32.63, 34.2, 34.5, 34.69, 34.79, 35.1, 35.4, 49.1, 49.3, 53.2, 53.4, 74.7, 74.8, 128.30, 128.37, 135.43, 135.48, 216.94, 216.96.



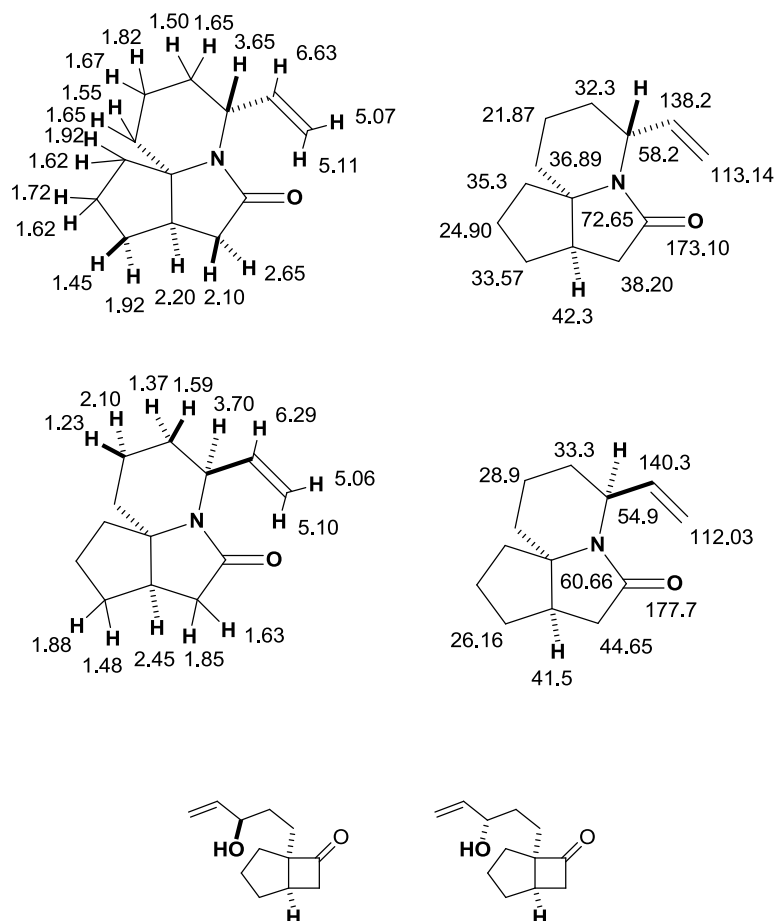
(1*R*,5*S*,*E*)-5-(6-Azidohept-4-enyl)bicyclo[3.2.0]heptan-6-one (1-193a), (1*R*,5*S*,*Z*)-5-(6-azidohept-4-enyl)bicyclo[3.2.0]heptan-6-one (1-193b), (1*R*,5*S*)-5-((*R*)-4-azidohept-5-enyl)bicyclo[3.2.0]heptan-6-one (1-193c), and (1*R*,5*S*)-5-((*S*)-4-azidohept-5-enyl)bicyclo[3.2.0]heptan-6-one (1-193d). A suspension of (1*R*,5*S*)-5-(6-bromohex-4-enyl)bicyclo[3.2.0]heptan-6-one (**(*R*)-1-192**) (145 mg, 0.540 mmol) and sodium azide (210

mg, 3.20 mmol) in DMF (3 mL) at room temperature was allowed to stir overnight. Diethyl ether and water were added and the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The resulting residue was purified by silica gel chromatography (0.2%-1% EtOAc/hexanes) to afford a mixture of azides **1-193a**, **1-193b**, **1-193c**, and **1-193d** as a colorless oil (110 mg, 88%, 65:9:13:13 ratio from ^1H NMR in acetone; 68:6:13:13 from ^1H NMR in CDCl_3). Azides **1-193a**, **1-193b**, **1-193c**, and **1-193d**: $[\alpha]_{546}^{25} -78.8$ (c 4.4, dichloromethane); $R_f = 0.40$ (10% EtOAc/hexanes); IR (neat) 2942, 2098, 1771, 1247 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{26}\text{H}_{38}\text{N}_4\text{O}_2+\text{H})^+$ 439.3073 (corresponding to $(2\text{M}-\text{N}_2+\text{H})^+$), found: 439.3075. Azide **1-193a**: ^1H NMR (400 MHz, acetone) δ 1.36-1.44 (m, 2H), 1.53-1.71 (m, 5H), 1.78-1.85 (m, 3H), 1.88-1.96 (m, 1H), 2.08-2.18 (m, 1H), 2.43 (dd, $J = 4.4$ Hz, 18.4 Hz, 1H), 2.54-2.64 (m, 1H), 3.13 (dd, $J = 9.6$ Hz, 18.4 Hz, 1H), 3.77 (d, $J = 6.4$ Hz, 2H), 5.55-5.63 (m, 1H), 5.79-5.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.98 (CH_2), 25.03 (CH_2), 32.55 (CH_2), 32.58 (CH_2), 32.68 (CH_2), 34.1 (CH), 35.3 (CH_2), 49.3 (CH_2), 52.8 (CH_2), 75.7 (C), 123.4 (CH), 136.3 (CH), 217.8 (C). Azide **1-193b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.90 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 122.52, 136.14. Azides **1-193c** and **1-193d** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 4.00 (q, $J = 6.8$ Hz, 1H), 5.27-5.36 (m, 2H), 5.79-5.86 (m, 1H). Azides **1-193b**, **1-193c** and **1-193d** (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 64.81 (CH), 64.84 (CH_2), 118.2 (CH_2), 135.6 (CH).



(**4R,7aR,10aS**)-4-Vinyl-octahydrocyclopenta[*i*]indolizin-6(7*H*)-one (**1-194**) and (**4S,7aR,10aS**)-4-vinyl-octahydrocyclopenta[*i*]indolizin-6(7*H*)-one (**1-195**). To a refluxing solution of azides **1-193a**, **1-193b**, **1-193c**, and **1-193d** (110 mg, 0.470 mmol) in anhydrous 1,2-dichloroethane (24 mL) under N₂ atmosphere was added titanium tetrachloride (0.71 mL, 1 M in dichloromethane, 0.71 mmol). After being allowed to reflux for 15 h, saturated aqueous ammonium chloride was added to the cooled reaction mixture, which was allowed to stir overnight. The aqueous layer was washed twice with dichloromethane. The aqueous layer was neutralized by saturated aqueous sodium bicarbonate and extracted twice with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine, and were dried over anhydrous sodium sulfate. The concentrated residue was purified by silica gel chromatography (10% EtOAc/hexanes) to afford **1-194** as a colorless oil (60 mg, 62%) and **1-195** as a colorless oil (6 mg, 6%). Lactam **1-194**: $[\alpha]_{546}^{25} +21.6$ (*c* 2.0, dichloromethane); $R_f = 0.50$ (100% EtOAc/hexanes, twice); IR (neat) 2937, 1683, 1401 cm⁻¹; HRMS (ESI) m/z calculated for (C₁₃H₁₉NO+H)⁺ 206.1545, found: 206.1522; ¹H NMR (400 MHz, CDCl₃) δ 1.42-1.55 (m, 3H), 1.58-1.77 (m, 6H), 1.78-1.85 (m, 1H), 1.85-1.95 (m, 2H), 2.08 (ddd, $J = 1.2$ Hz, 4.0 Hz, 17.6 Hz, 1H), 2.15-2.23 (m, 1H), 2.64 (dd, $J = 10.4$ Hz, 17.6 Hz, 1H), 3.66 (t, $J = 8.8$ Hz, 1H), 5.06-5.13 (m, 2H), 6.58-6.67 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 21.9 (CH₂), 24.9 (CH₂), 32.3 (CH₂), 33.6 (CH₂), 35.3 (CH₂), 36.9 (CH₂), 38.2 (CH₂), 42.3 (CH), 58.2 (CH), 72.7 (C), 113.1 (CH₂), 138.3 (CH), 173.1 (C). Lactam **1-195**: $R_f = 0.55$ (100% EtOAc/hexanes, twice); IR (neat) 2937, 1698, 1388 cm⁻¹; HRMS (ESI) m/z calculated for (C₁₃H₁₉NO+H)⁺ 206.1545, found: 206.1515; ¹H NMR (400

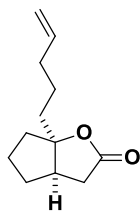
MHz, CDCl₃) δ 1.19-1.27 (m, 1H), 1.36-1.47 (m, 4H), 1.58-1.75 (m, 6H), 1.84-1.87 (m, 2H), 2.05-2.09 (m, 1H), 2.45 (t, J = 5.2 Hz, 1H), 3.67-3.72 (m, 1H), 5.05-5.12 (m, 2H), 6.25-6.33 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 18.85 (CH₂), 18.89 (CH₂), 26.2 (CH₂), 28.9 (CH₂), 33.3 (CH₂), 35.2 (CH₂), 41.5 (CH), 44.7 (CH₂), 54.9 (CH), 60.7 (C), 112.0 (CH₂), 140.3 (CH), 177.8 (C). The following data were used to assign lactams **1-194** and **1-195**.



(1*R,5*S**)-5-((*S**)-3-Hydroxypent-4-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-201)**

and **(1*R**,5*S**)-5-((*R**)-3-hydroxypent-4-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-201)**. To a suspension of SeO₂ (22 mg, 0.20 mmol) and salicylic acid (28 mg, 0.20 mmol) in dichloromethane (2 mL) at 0 °C under N₂ atmosphere was added slowly TBHP (5 M in hexane, 0.15 mL, 0.75 mmol). After the reaction mixture was stirred for 20 min, a solution of

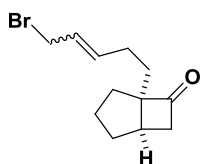
cyclobutanone **1-112** (178 mg, 1.00 mmol) in dichloromethane (2 mL) was added. The resulting mixture was stirred overnight, and 10% aqueous KOH solution and diethyl ether were added. After the separation, the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine and dried over sodium sulfate. The concentrated residue was purified by chromatography (0.5-10% EtOAc/hexanes) to afford a mixture of cyclobutanone **1-201** (2:1 ratio (arbitrarily assigned), 15 mg, 8%) as a colorless oil and lactone **1-202** (32 mg, 16%) as a colorless oil. Ketone **1-201** (2:1 ratio): R_f = 0.30 (20% EtOAc/hexanes); IR (neat) 3420, 2939, 1764, 1065 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{36}\text{O}_4\text{Na}$ ($2\text{M}+\text{Na}$)⁺ 411.2511, found: 411.2515. Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.40 (dt, J = 6.4 Hz, 9.6 Hz, 1H), 1.51-1.58 (m, 1H), 1.63-1.75 (m, 4H), 1.75-1.90 (m, 3H), 2.02-2.09 (m, 1H), 2.46 (dd, J = 4.6 Hz, 18.4 Hz, 1H), 2.53-2.63 (m, 1H), 3.13 (dd, J = 9.6 Hz, 18.4 Hz, 1H), 4.06-4.16 (m, 1H), 5.11-5.26 (m, 2H), 5.82-5.91 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.98 (CH_2), 28.8 (CH_2), 32.7 (CH_2), 32.9 (CH_2), 34.1 (CH), 35.4 (CH_2), 49.2 (CH_2), 73.2 (CH), 75.4 (C), 115.0 (CH_2), 140.8 (CH), 218.0 (C). Minor isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.14 (dd, J = 9.6 Hz, 18.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.01 (CH_2), 28.7 (CH_2), 32.8 (CH_2), 34.2 (CH), 35.1 (CH_2), 49.1 (CH_2), 73.1 (CH), 75.3 (C), 140.78 (CH), 217.9 (C).



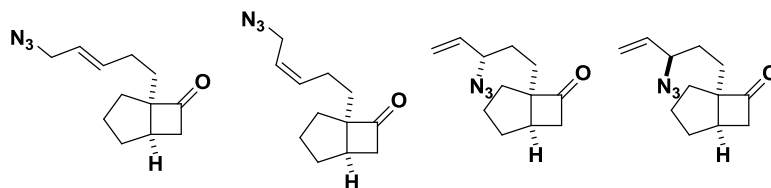
(3aR*,6aR*)-6a-(Pent-4-en-1-yl)hexahydro-2H-cyclopenta[b]furan-2-one (1-202).

Lactone **1-202**: R_f = 0.40 (20% EtOAc/hexanes); IR (neat) 2942, 1763, 1189 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{36}\text{O}_4\text{Na}$ ($2\text{M}+\text{Na}$)⁺ 411.2511, found: 411.2512; ^1H NMR (400 MHz, CDCl_3) δ 1.48-1.60 (m, 4H), 1.61-1.78 (m, 4H), 1.87-1.93 (m, 1H), 2.06-2.11 (m, 3H),

2.30 (dd, $J = 2.6$ Hz, 18.4 Hz, 1H), 2.50-2.58 (m, 1H), 2.87 (dd, $J = 10.4$ Hz, 18.4 Hz, 1H), 4.97-5.05 (m, 2H), 5.76-5.85 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.5 (CH_2), 24.0 (CH_2), 33.8 (CH_2), 34.4 (CH_2), 37.0 (CH_2), 38.1 (CH_2), 38.8 (CH_2), 42.2 (CH), 98.0 (C), 115.1 (CH_2), 138.1 (CH), 177.4 (C).



(1R*,5S*)-5-(5-Bromopent-3-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-197). To a suspension of cyclobutanone **1-112** (520 mg, 2.92 mmol) and NBS (623 mg, 3.50 mmol) in carbon tetrachloride (30 mL) at refluxing temperature under N_2 temperature was added catalytic amount of BPO. The heating was continued for 2 h. After the resulting mixture was cooled to room temperature, the solvent was removed under reduced temperature. The concentrated residue was purified by chromatography (0.5% EtOAc/hexanes) to afford bromide **1-197** (460 mg, 61%, E/Z : 6:1) as a colorless oil. Bromide **1-197** (6:1 ratio): $R_f = 0.30$ (10% EtOAc/hexanes); IR (neat) 2946, 1765, 1204 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{33}\text{BrO}_2\text{Na}$ ($2\text{M-HBr}+\text{Na}$) $^+$ 455.1562, found: 455.1557. Bromide E -isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.38 (td, $J = 12.6, 6.3$ Hz, 1H), 1.65-1.75 (m, 3H), 1.76-1.89 (m, 3H), 2.02 (dd, $J = 12.8, 6.3$ Hz, 1H), 2.05-2.13 (m, 1H), 2.20-2.29 (m, 1H), 2.42-2.50 (m, 1H), 2.54-2.63 (m, 1H), 3.13 (dd, $J = 18.5, 9.5$ Hz, 1H), 3.94 (d, $J = 6.6$ Hz, 1H), 5.65-5.81 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.9 (CH_2), 28.4 (CH_2), 32.2 (CH_2), 32.7 (CH_2), 33.3 (CH_2), 34.1 (CH), 35.4 (CH_2), 49.3 (CH_2), 75.3 (C), 126.6 (CH), 135.7 (CH), 217.4 (C). Bromide Z -isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.99 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.4 (CH_2), 27.0 (CH_2), 125.7 (CH), 135.0 (CH).



(1*R,5*S**)-5-((*E*)-5-Azidopent-3-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-198a),**

(1*R,5*S**)-5-((*Z*)-5-azidopent-3-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-198b), (1*R**,5*S**)-5-**

((*S)-3-azidopent-4-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-198c), and (1*R**,5*S**)-5-((*R**)-3-**

azidopent-4-en-1-yl)bicyclo[3.2.0]heptan-6-one (1-198d). According to the procedure

described for azides **1-193a**, **1-193b**, **1-193c**, and **1-193d**, bromide **1-197** (480 mg, 0.187 mmol) afforded by silica gel chromatography (0.2%-1% EtOAc/hexanes) a mixture of azides

1-198a, **1-198b**, **1-198c**, and **1-198d** as a colorless oil (173 mg, 42%, 63:7:15:15 ratio from

¹H NMR in acetone; 65:7:14:14 from ¹H NMR in CDCl₃). Azides **1-198a**, **1-198b**, **1-198c**,

and **1-198d**: *R_f* = 0.50 (10% EtOAc/hexanes); IR (neat) 2947, 2093, 1766 cm⁻¹; HRMS (ESI)

m/z calculated for C₁₂H₁₇N₃ONa (M+Na)⁺ 242.1269, found: 242.1252. Azide **1-198a**: ¹H

NMR (400 MHz, acetone) δ 1.44 (td, *J* = 12.6, 6.2 Hz, 1H), 1.63-1.76 (m, 3H), 1.80-1.87 (m,

3H), 1.94 (dd, *J* = 12.6, 6.5 Hz, 1H), 2.04-2.15 (m, 1H), 2.23-2.32 (m, 1H), 2.44 (dd, *J* = 18.3,

4.5 Hz, 1H), 2.56-2.67 (m, 1H), 3.16 (dd, *J* = 18.3, 9.6 Hz, 1H), 3.77 (d, *J* = 6.5 Hz, 2H), 5.61

(dtt, *J* = 14.8, 6.6, 1.4 Hz, 1H), 5.76-5.89 (m, 1H); ¹³C NMR (100 MHz, acetone) δ 24.7

(CH₂), 28.3 (CH₂), 32.3 (CH₂), 32.5 (CH₂), 33.9 (CH), 34.9 (CH₂), 48.9 (CH₂), 52.3 (CH₂),

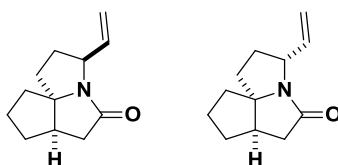
75.3 (C), 123.4 (CH), 136.1 (CH), 215.3 (C). Azide **1-198b** (diagnostic peaks only): ¹H NMR

(400 MHz, acetone) δ 3.91 (d, *J* = 7.3 Hz, 2H); ¹³C NMR (100 MHz, acetone) δ 122.5 (CH),

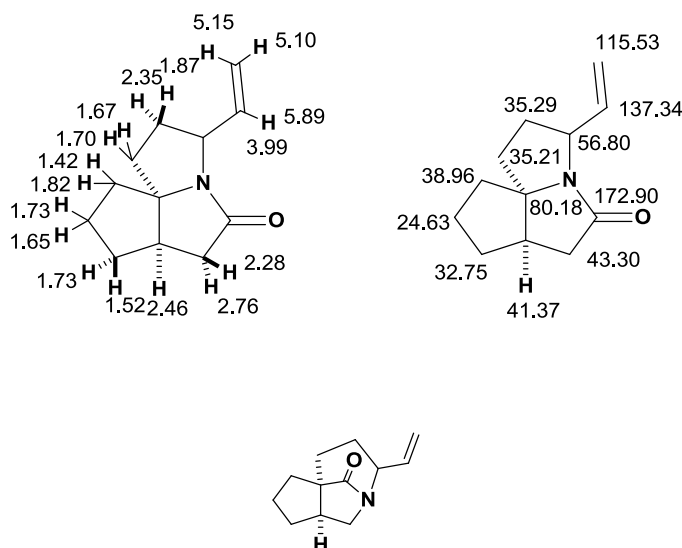
135.4 (CH). Azides **1-198c** and **1-198d** (diagnostic peaks only): ¹H NMR (400 MHz, acetone)

δ 3.95-4.01 (m, 1H), 5.28-5.37 (m, 2H), 5.76-5.89 (m, 1H); ¹³C NMR (100 MHz, acetone) δ

65.0 (CH), 117.7 (CH₂), 117.8 (CH₂), 135.89 (CH), 135.93 (CH), 215.1 (C).

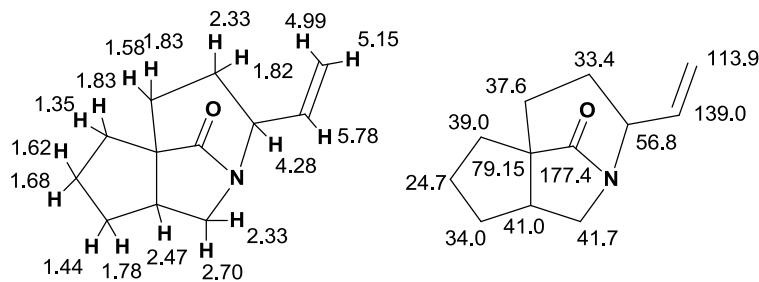


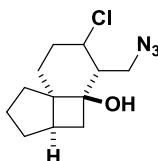
(**3*S*^{*},6*aR*^{*},9*aS*^{*}**)-3-Vinylhexahydro-1*H*-cyclopenta[*g*]pyrrolizin-5(6*H*)-one (**1-199**) and (**3*R*^{*},6*aR*^{*},9*aS*^{*}**)-3-Vinylhexahydro-1*H*-cyclopenta[*g*]pyrrolizin-5(6*H*)-one (**1-200**). According to the procedure described for lactam **1-194**, azides **1-198a**, **1-198b**, **1-198c**, and **1-198d** (58 mg, 0.26 mmol) afforded after chromatography a mixture of twisted lactam **1-201** (one isomer) and azide **1-202** (5:3 ratio, 3 mg), and a mixture of lactams **1-199**, **1-200** and azide **1-202** (2.1:1:1 ratio, 13 mg). (Their stereochemistry is not defined) Lactam **1-199** (or **1-200**, major isomer): R_f = 0.35 (100% EtOAc/hexanes); IR (neat) 2950, 1686, 1386 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{18}\text{NO}$ ($\text{M}+\text{H}$)⁺ 192.1388, found: 192.1393; ^1H NMR (500 MHz, CDCl_3) δ 1.37-1.45 (m, 1H), 1.48-1.52 (m, 1H), 1.59-1.66 (m, 2H), 1.68-1.75 (m, 3H), 1.78-1.88 (m, 2H), 2.29 (ddd, J = 17.6, 7.3, 1.3 Hz, 1H), 2.32-2.39 (m, 1H), 2.43-2.49 (m, 1H), 2.74 (dd, J = 17.6, 10.6 Hz, 1H), 3.99 (t, J = 8.7 Hz, 1H), 5.08-5.11 (m, 1H), 5.16 (dt, J = 17.1, 1.0 Hz, 1H), 5.89 (ddd, J = 17.1, 10.2, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 24.6 (CH_2), 32.8 (CH_2), 35.3 (CH_2), 35.7 (CH_2), 39.0 (CH_2), 41.4 (CH), 43.3 (CH_2), 56.8 (CH), 80.2 (C), 115.5 (CH), 137.3 (CH_2), 172.9 (C). Lactam **1-200** (or **1-199**, minor isomer) (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 2.07-2.13 (m, 1H), 2.70-2.73 (m, 1H), 4.17 (t, J = 7.7 Hz, 1H), 5.88 (ddd, J = 17.2, 10.3, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.1 (CH_2), 24.9 (CH_2), 31.9 (CH_2), 34.6 (CH_2), 46.0 (CH_2), 48.5 (CH), 54.5 (CH), 70.2 (C), 115.3 (CH_2), 136.9 (CH), 173.5 (C) [or 173.8 (C)]. The following data were used to assign lactam **1-200** (or **1-199**).



(5a*S,8a*S**)-3-Vinyloctahydro-2,5a-methanocyclopenta[*c*]azepin-9-one (1-201).**

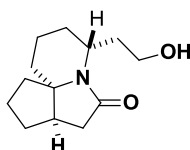
Lactam **1-201**: R_f = 0.55 (10% EtOAc/hexanes, twice); IR (neat) 2953, 1690 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{17}\text{NONa}$ ($\text{M}+\text{Na}$) $^{+}$ 214.1208, found: 214.1208; ^1H NMR (500 MHz, CDCl_3) δ 1.30-1.37 (m, 1H), 1.47-1.51 (m, 1H), 1.56-1.64 (m, 2H), 1.65-1.72 (m, 1H), 1.72-1.85 (m, 4H), 2.29-2.37 (m, 2H), 2.43-2.49 (m, 1H), 2.70 (dd, J = 17.6, 10.6 Hz, 1H), 4.28 (q, J = 7.8 Hz, 1H), 4.99 (dt, J = 10.3, 1.5 Hz, 1H), 5.15 (dt, J = 17.0, 1.5 Hz, 1H), 5.78 (ddd, J = 17.0, 10.3, 5.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 24.7 (CH_2), 33.4 (CH_2), 34.0 (CH_2), 37.6 (CH_2), 39.0 (CH_2), 41.0 (CH), 41.7 (CH_2), 56.8 (CH), 79.2 (CH), 113.9 (CH_2), 139.0 (CH), 177.4 (C). The following data were used to assign lactam **1-201**.





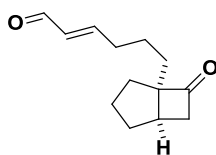
(3aR*,4aR*,5R*,8aS*)-5-(Azidomethyl)-6-chlorodecahydrocyclopenta-[1,4]

cyclobuta-[1,2]benzen-4a-ol (1-202). Azide **1-202** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.68 (s, 1H), 3.70-3.74 (m, 1H), 4.23-4.27 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 63.3 (CH_2), 69.3 (CH_2), 70.6 (CH_2).

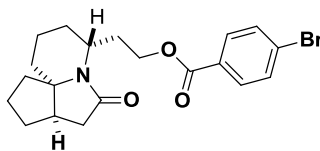


(4R,7aR,10aS)-4-(2-Hydroxyethyl)-octahydrocyclopenta[i]indolizin-6(7H)-one

(1-58). To an oven-dried flask at 0 °C under nitrogen atmosphere was added $\text{BH}_3 \cdot \text{THF}$ complex (1 M in THF, 1.25 mL, 1.25 mmol), followed by the addition of 2-methyl-2-butene (2 M in THF, 1.25 mL, 2.50 mmol). After stirring at 0 °C for 2 h, the above solution was added to lactam **1-194** (40 mg, 0.20 mmol) in THF (2 mL) at 0 °C. The resulting reaction mixture was allowed to rise to room temperature and stir overnight. The resulting mixture was cooled to 0 °C, followed by the addition of 3 M aqueous NaOH (2.1 mL) and H_2O_2 (30% w/w in H_2O , 1 mL). The resulting reaction mixture was allowed to rise to room temperature over 2 h. Ethyl acetate was used to extract the product. The aqueous layer was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (0.8%-2% MeOH/dichloromethane) to afford lactam **1-58** (35 mg, 83%) as an oil. $[\alpha]_{546}^{25} -22.6$ (c 0.9, dichloromethane). $R_f = 0.35$ (5% MeOH/DCM); spectral data matched with reported data.¹⁵



(E)-6-((1S,5R)-7-oxobicyclo[3.2.0]heptan-1-yl)hex-2-enal (1-203). To a solution of cyclobutanone **1-112** (534 mg, 3.00 mmol) and acrolein (90% purity, 1.0 mL, 15 mmol) in dichloromethane (8 mL) under N₂ atmosphere at room temperature was slowly added Grubbs 2nd generation catalyst (305 mg, 0.030 mmol, 10 mol%). The reaction mixture was heated to reflux for 38 h. After the resulting mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (3%-15% EtOAc/hexanes) to afford compound **1-203** as an oil (230 mg, 37% (or 85% brsm)) and ketone **1-112** (300 mg). Ketone **1-203**: R_f = 0.25 (20% EtOAc/hexanes); IR (neat) 2945, 1768, 1697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.36 (td, J = 12.6, 6.4 Hz, 1H), 1.45-1.53 (m, 1H), 1.59-1.72 (m, 4H), 1.77-1.87 (m, 3H), 2.02 (dd, J = 12.9, 6.1 Hz, 1H), 2.30-2.38 (m, 2H), 2.45 (dd, J = 18.5, 4.6 Hz, 1H), 2.55 (dt, J = 10.0, 5.1 Hz, 1H), 3.11 (dd, J = 18.5, 9.4 Hz, 1H), 6.10 (ddt, J = 15.6, 7.9, 1.3 Hz, 1H), 6.81 (dt, J = 15.6, 6.8 Hz, 1H), 9.49 (d, J = 7.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.0 (CH₂), 24.9 (CH₂), 32.6 (CH₂), 32.8 (CH₂), 33.0 (CH₂), 34.2 (CH), 35.3 (CH₂), 49.2 (CH₂), 75.5 (C), 133.3 (CH), 157.8 (CH), 193.9 (CH), 217.4 (C).



2-((4R*, 7aR*, 10aS*)-6-Oxodecahydrocyclopenta[i]indolizin-4-yl)ethyl 4-bromobenzoate (1-207). To a solution of 4-bromobenzoyl chloride (17 mg, 0.075 mmol) in anhydrous dichloromethane (2 mL) at room temperature under N₂ atmosphere was added DMAP (12 mg, 0.10 mmol). After the resulting mixture was stirred for 15 min, a solution of

alcohol **1-58** (10 mg, 0.050 mmol) in dichloromethane (1 mL) was slowly added. The resulting mixture was stirred overnight. Dichloromethane and saturated sodium bicarbonate were added to quench the reaction. After separation, the aqueous layer was extracted twice with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine, and were dried over anhydrous sodium sulfate. The concentrated residue was purified by silica gel chromatography (10%-30% EtOAc/hexanes) to afford ester **1-207** (7 mg, 38%) as a white powder. Lactam **1-207**: $[\alpha]_{546}^{25}$ -64.0 (*c* 0.35, dichloromethane); R_f = 0.50 (100% EtOAc/hexanes); IR (neat) 2932, 1719, 1679, 1271 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{25}\text{BrNO}_3$ ($\text{M}+\text{H}$)⁺ 406.1018, found: 406.1021; ^1H NMR (400 MHz, CDCl_3) δ 1.37-1.43 (m, 1H), 1.46-1.73 (m, 8H), 1.77-1.88 (m, 2H), 1.92-2.01 (m, 1H), 2.01-2.12 (m, 2H), 2.12-2.20 (m, 1H), 2.64 (dd, J = 17.6, 9.7 Hz, 1H), 3.19 (ddd, J = 14.0, 10.0, 5.0 Hz, 1H), 3.24-3.33 (m, 1H), 4.43-4.54 (m, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.0 (CH_2), 25.3 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 33.8 (CH_2), 35.1 (CH_2), 36.5 (CH_2), 38.2 (CH_2), 42.0 (CH), 52.9 (CH), 63.9 (CH_2), 73.7 (C), 127.9 (C), 129.4 (C), 131.1 (CH), 131.7 (CH), 165.8 (C), 174.0 (C).

CHAPTER 2

COMBINED ALLYLIC AZIDE REARRANGEMENT AND INTRAMOLECULAR SCHMIDT REACTION

2.1 Introduction

Intramolecular Schmidt reaction. The intramolecular Schmidt reaction of alkyl azides and ketones was discovered in 1991 as a method to prepare polycyclic lactams (Figure 35).^{68,69} This reaction has been applied by our group and other groups to the total syntheses of natural products such as stenine,²² aspidospermidine,⁷⁰ alkaloids 223A²⁴ and 251F.⁷¹ The diversification of these polycyclic lactams such as stenine can also help to find some hit or lead compounds with interesting biological activities.

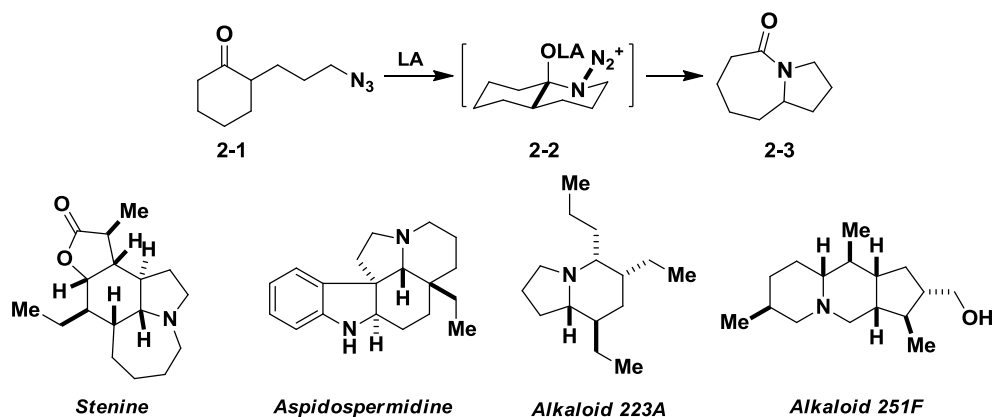


Figure 35. Intramolecular Schmidt reaction.

The detailed mechanism of intramolecular Schmidt reaction is listed in Figure 36. There are four possible pathways, three of which lead to normal fused bicyclic lactam 2-3 and

one of which produces twisted amide **2-12**. For equatorial side chain conformer **2-4**, azide can attack the ketone from both faces. Recently, Tantillo and coworkers reported a computational analysis of the intramolecular Schmidt reaction.⁷² The azidohydrin intermediate is ~9–10 kcal/mol lower than the protonated starting material. The transition state from azidohydrin to lactam is 5–7 kcal/mol higher than the protonated ketones. The lactam **2-3** is ~70–80 kcal/mol lower than azidohydrin intermediates.

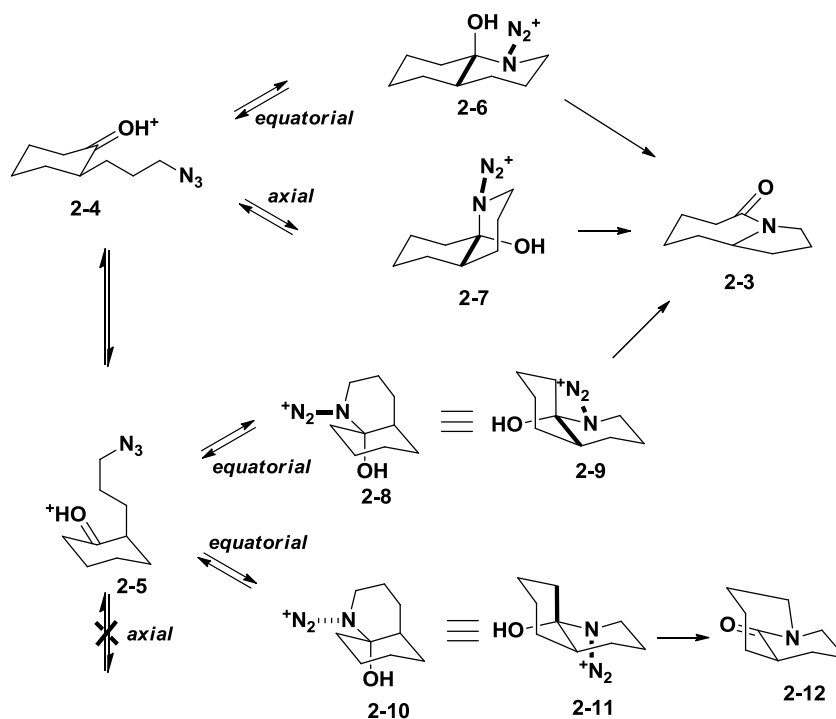


Figure 36. Plausible mechanism of intramolecular Schmidt reaction.

If α -substituent of the ketone can stabilize the diazonium ion via cation- n or cation- π interaction, twisted amide **2-12** could become the major product.^{73,74} Such lactams have unique properties, as briefly reviewed below.

Twisted amides. The amide is one of the basic functional groups in organic chemistry, and has arisen many fundamental interests in structural organic chemistry and biological chemistry. The traditional amide bond is generally planar, resulting from

conjugation of the nitrogen lone pair with the π orbital of carbonyl group (Figure 37). This delocalization leads to a weakened double bond and a strengthened C–N bond with partial double bond characters, which are reflected in low reactivities, protonation at oxygen atom instead of nitrogen atom, and tolerance to hydrolysis.⁷⁵ The rotation of C–N bond is also hindered and its *E/Z* isomerization energy is relatively high, about 20 kcal/mol. Twisting of this C–N bond restricts the delocalization of carbonyl with nitrogen, and thus leads to a new breed of amides, referred to twisted amides.^{75,76} Winkler-Dunitz parameters, used to describe how twisted the amide is, are calculated as designated in Figure 37.⁷⁷

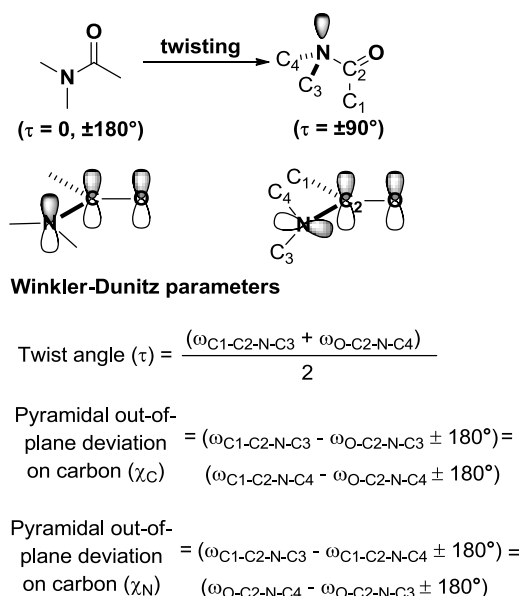


Figure 37. Comparison of normal and twisted amides.

Twisted amide can be obtained by embedding an amide bond into a bicyclic or tricyclic ring system, which can force the amide bond have no choice but to exist in a highly destabilized manner. Some well-known twisted amides are shown in Figure 38.⁷⁸⁻⁸³ Kirby's amide is known as "most twisted amide".⁷⁸

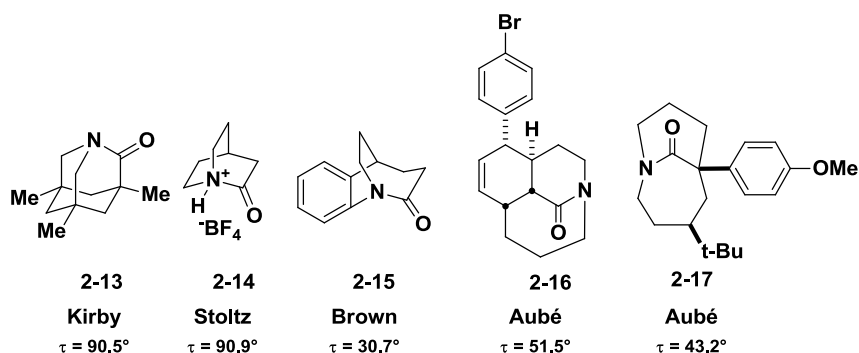


Figure 38. The most well-known twisted amides.

Twisted amide has a different physical and spectral profile from traditional amide (Table 6). Twist angle ranges from 0° to 90° , and the N-C(O) bond is longer than a traditional amide and shorter than an amine. However, there is no big difference for the bond length of carbonyl group. The stretching frequency and carbon NMR chemical shift of carbonyl group range from those of traditional amide to those of ketone. Their ionization potentials are also different.

Table 6. Physical and spectral parameters of amides.

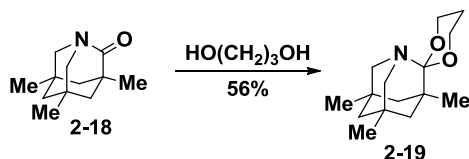
Substrate	$\tau/^\circ$	$\chi_N/^\circ$	$\chi_C/^\circ$	N-C(O) /Å	C=O /Å	$\nu_{C=O}$ /cm ⁻¹	$^{13}\text{C}_{(C=O)}$ /ppm
ethylamine	-	-	-	1.47	-	-	-
acetamide	-	-	-	1.38	1.22	1681	178
acetone	-	-	-	-	1.213	1749	207
1-methylpiperidin-2-one	2.5	0.0	0.0	1.325	1.233	1653	165
Kirby (2-13)	90.5	60.0	0.0	1.475	1.196	1732	200
Aubé (2-16)	51.5	36.1	12.8	1.387	1.218	1697	188
Aubé (2-17)	43.2	33.8	16.3	1.363	1.234	1685	185

This twist of amide bond is coupled with formal rehybridization of nitrogen to sp^3 , which gives this nitrogen a pyramidal configuration. In comparison with traditional amides, the nitrogen of twisted amide is more basic. Its carbonyl group also has some ketone character.

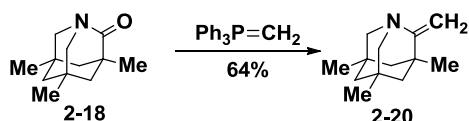
The most common comparison between twisted amides and traditional amides is hydrolysis of the amide bond.⁸⁴ The half-life for hydrolysis of Kirby's and Stoltz's twisted amides is less than 10 minutes, while it is around 500 years for traditional amides.

These novel reactivities of twisted amides have been explored to allow them to take part in reactions that are not possible with traditional amides, such as ketal formation,⁸⁰ facile reduction,⁸⁵ oxidative cleavage,⁸³ epoxidation,⁸⁶ Wittig reaction,⁸⁰ hydrogenation,⁸³ ammonium salt formation,⁸⁷ and nucleophilic addition (Figure 39).⁸⁵

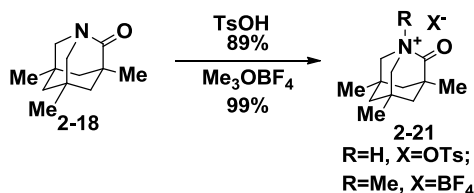
Ketal formation



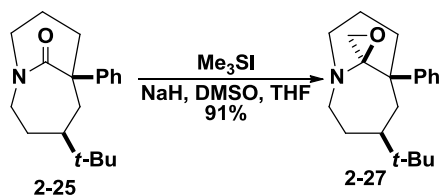
Wittig reaction



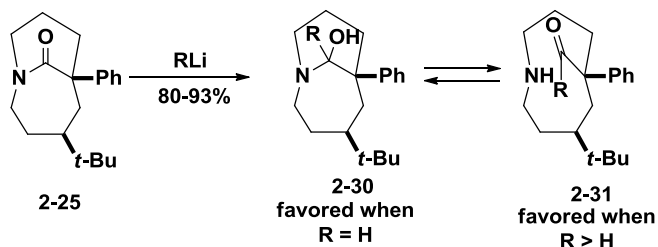
Ammonium salt formation



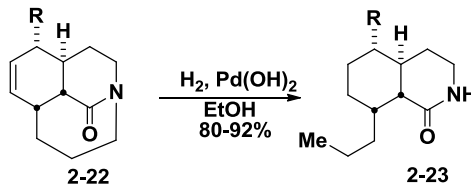
Epoxidation



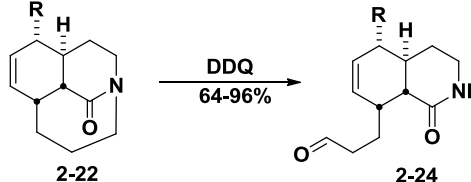
Nucleophilic addition



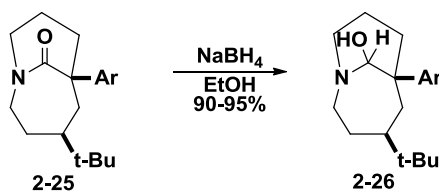
Hydrogenation



Oxidative cleavage



Reduction



Hydrazone formation

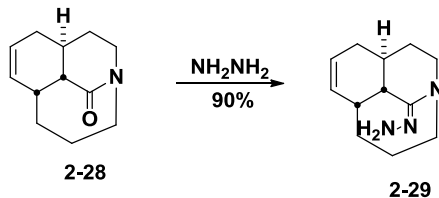


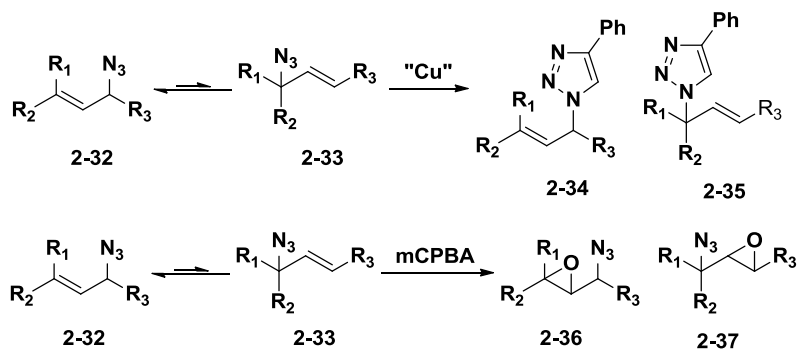
Figure 39. The novel reactivities of twisted amide.

Allylic azide rearrangement. The rearrangement of allylic azides has been known since 1960, when it was first reported by Winstein and coworkers.⁸⁸ They found that crotyl azide rearranges reversibly to give α -methylallyl azide and γ,γ -dimethylallyl azide give α,α -dimethylallyl azide. They demonstrated that the methyl substitution only increases the rate of equilibration by about 3 times, and this rate is only increased by 10 times even if the solvent

is changed from pentane to 70% aqueous acetone. It is also interesting to know that allylic azide is not solvolysed, even in 70% aqueous acetone. They also observed a ΔS value around -10 eu for isomerization of α,α -dimethylallyl azides in different solvent systems. Winstein and coworkers also indicated the small change of polar character and small solvent effect in the azide isomerization, indicating the covalent bonding in the transition state.

VanderWerf and Heasley from the University of Kansas reported the rearrangement of allylic diazides, and found that electron-withdrawing group destabilizes this transition state and then the rate of rearrangement is also decreased.⁸⁹ The transition state was described by them, best as a nearly planar, six-membered ring.

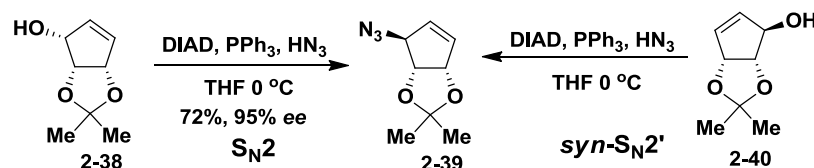
Fokin, Sharpless, and coworkers reported the Huisgen [3+2] cycloaddition and epoxidation reactions of isomeric allylic azides (Scheme 54).⁹⁰ Reactivities of different types of allylic azides were compared to find that tertiary azides were more reactive than those of primary and secondary azides. However, there was no big difference in the reaction rate between primary and secondary azides for both reactions. They also found that H-bonding could have an important effect on these allylic azide systems.



Scheme 54. Huisgen [3+2] cycloaddition and epoxidation of allylic azides.

Carell and coworkers reported an unusual discovery about the preparation of allylic azide from allylic alcohol via S_N2 and syn- S_N2' pathways (Scheme 55).⁹¹ The 1,3-transposed

product of **2-39** is also its enantiomer, and thus this makes the determination of its isomerization rate easier. They used optical rotation to track its isomerization rate at different temperatures, and observed that allylic azide rearrangement is almost inhibited at 0 °C.



Scheme 55. Preparation of allylic azide through S_N2 and *syn*-S_N2' pathways.

Spino and coworkers found that *p*-menthane-3-carboxaldehyde is a useful chiral auxiliary in organic synthesis, especially for the total synthesis of alkaloids.⁹² Allylic alcohol **2-42** was prepared with very high selectivity employing trimethyl aluminum as the catalyst, and the following anti-S_N2' Mitsunobu reaction also provided allylic azide **2-43** with very high diastereoselectivity.^{93,94} This allylic azide has been used in the total syntheses of alkaloids such as coniine,⁹⁴ lentiginosin,⁹⁴ pumiliotoxin,⁹⁴ aspidofractinine,⁹⁵ euphococcintine, and adaline.⁹⁶

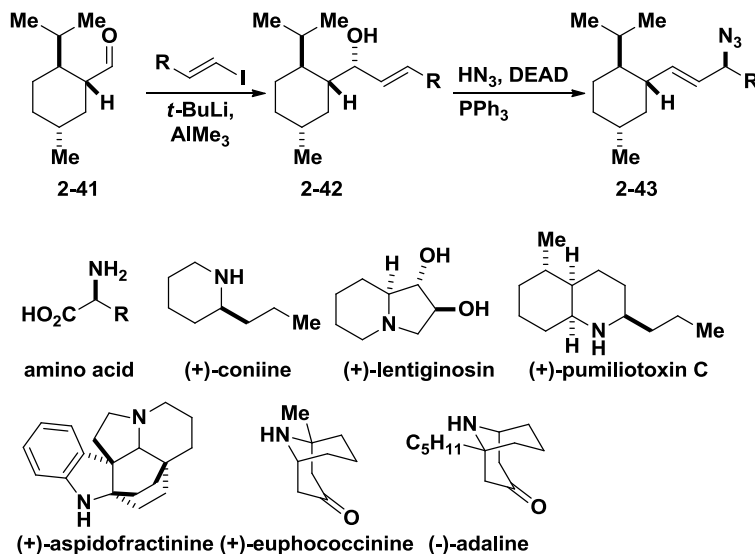
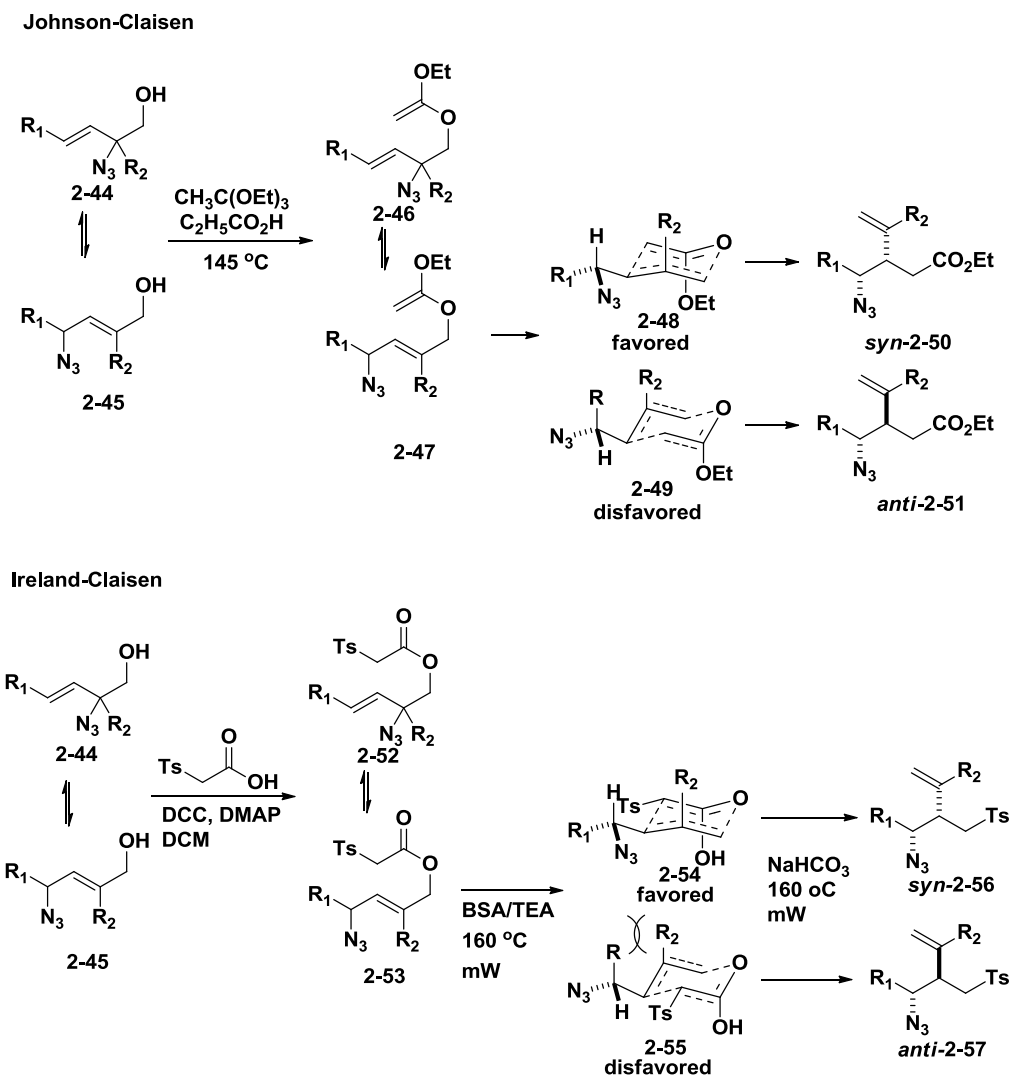


Figure 40. Spino's allylic azide and its application in the synthesis.

Recently, Craig and coworkers reported the combination of allylic azide rearrangement and different types of Claisen rearrangements (Scheme 56).⁹⁷ The equilibrating process of isomeric allylic azides was terminated by the subsequent Claisen rearrangement, in which only two isomers of allylic azides can proceed. In the Johnson-Claisen reaction, they proposed that only *E*-isomer **2-47** of allylic azides was existed in the equilibrium, and was the only isomer that contributed to the Claisen reaction. The conformation of *E*-isomer forces the R₂ group of transition states **2-48** and **2-49** to the pseudo-axial position. The different orientation of azide stereochemistry, in combination with axial R₂ group, can differentiate both transitions state. Actually, they did not get good selectivity for this combination (Table 7). A slightly better selectivity was obtained for the combination of allylic azide rearrangement with Ireland-Claisen reaction.



Scheme 56. Combination of allylic azide rearrangement and Claisen reaction.

Table 7. Johnson and Ireland-Claisen reactions.

entry	R ₁	R ₂	syn:anti	syn:anti
			(Johnson-Claisen)	(Ireland-Claisen)
a	<i>n</i> -C ₅ H ₁₁	H	50:50	84:16
b	<i>n</i> -C ₅ H ₁₁	Me	59:41	68:32

c	Me	Me	60:40	91:9
d	<i>c</i> -Hex	Me	63:37	82:18
e	Ph	H	-	75:25
f	2-Pyridyl	Me	-	-
g	Me	Ph	50:50	73:27

The allylic azide rearrangement allows for the existence of *Z*-isomer **2-58** of isomeric allylic azides, if only in small amount. If the temperature increases, the proportion of **2-58** also increases. Despite this, Craig and coworkers did not take the *Z*-isomer into consideration (Figure 41), nor did they run temperature-variable NMR experiments to make sure that there is no *Z*-isomer involved in the diethoxyethene stage at high temperature. The *Z*-isomer transition state should be much stable than those having *E* isomers because its R_2 appendage of the former lies at the pseudo-equatorial position of transition state. This can explain why Ireland-Claisen got higher selectivity than Johnson-Claisen rearrangement because both equatorial groups of Ireland-Claisen magnify the difference of azide stereochemistry.

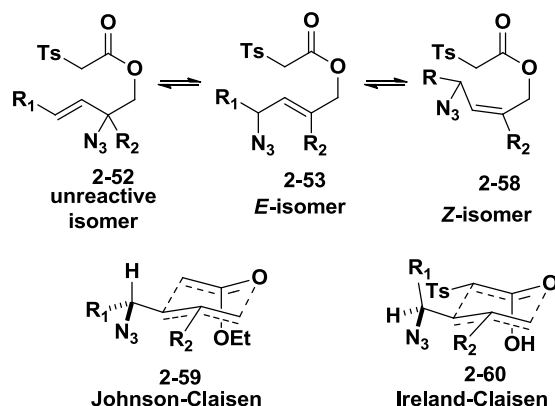
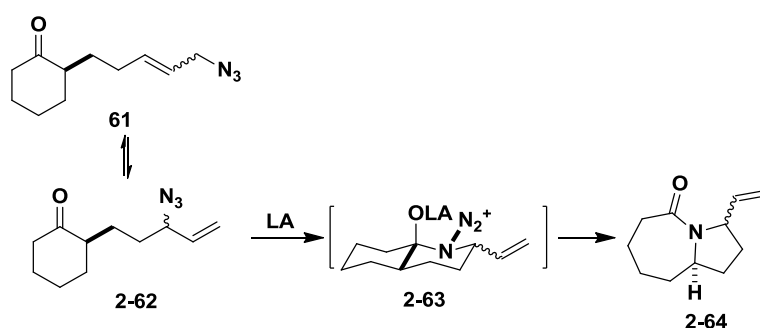


Figure 41. Intermediates in the Johnson and Ireland-Claisen reactions.

2.2 Combined allylic azide rearrangement and intramolecular Schmidt reaction

In our planning for the synthesis of pinnaic acid's advanced intermediate, we imagined whether allylic azide rearrangement and Schmidt reaction could be combined. The initial studies in the pinnaic acid project verified the feasibility of this combination reaction. Because that substrate belongs to four-carbon tethered Schmidt reaction, three-carbon tethered version, the more common one of Schmidt reaction, was investigated here (Scheme 57).



Scheme 57. Combination of allylic azide rearrangement and intramolecular Schmidt reaction.

Based on the Curtin-Hammett principle and early transition state theory (Figure 42), we hypothesized that: 1) four isomers of allylic azides would equilibrate faster than the Schmidt reaction would occur; 2) the azide of *E*-isomer of allylic azides can not reach the carbonyl to form productive azidohydrin intermediate; 3) for *Z*-isomer of allylic azides, the formation of an 8-membered azidohydrin ring, resulted from the attack of azide to carbonyl group, is relatively slow, in comparison with the formation of 6-membered ring from two internal isomers; 4) formation of lactams would be kinetically controlled via the preferential formation of intermediates **I** and **II** (both arising from equatorial attack of azide onto ketone); and 5) the stereochemical outcome of the reaction would roughly reflect the relative stability of **I** and **II**, favoring compound **2-66a** by a ratio that would roughly reflect the A value of a

vinyl group (1.49 or 1.68 kcal/mol), or $\geq 93:7$ dr. So a highly diastereoselective ratio would be expected.

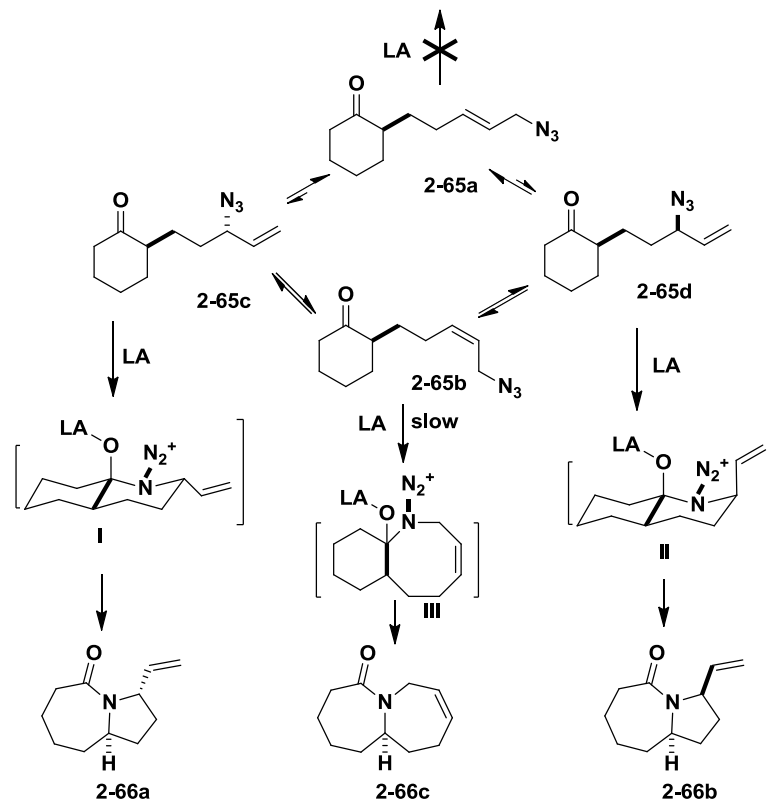


Figure 42. Mechanism of combination of allylic azide rearrangement and intramolecular reaction.

2.3 Allylic azide preparation

Allylic azides are usually prepared from the azide displacement of its corresponding bromide, which can be obtained from two methods: direct allylic bromination or cross-metathesis (Figure 43). Initially, NBS-mediated allylic bromination was used under the radical initiator benzoyl peroxide to get bromide **2-68**, and some dibromo products were found as sideproducts. Better result was obtained by the cross-metathesis using HG-2 as the

catalyst between olefin and allyl bromide. Later, it was found that cross-metathesis and azide displacement can be combined in a one-pot reaction.

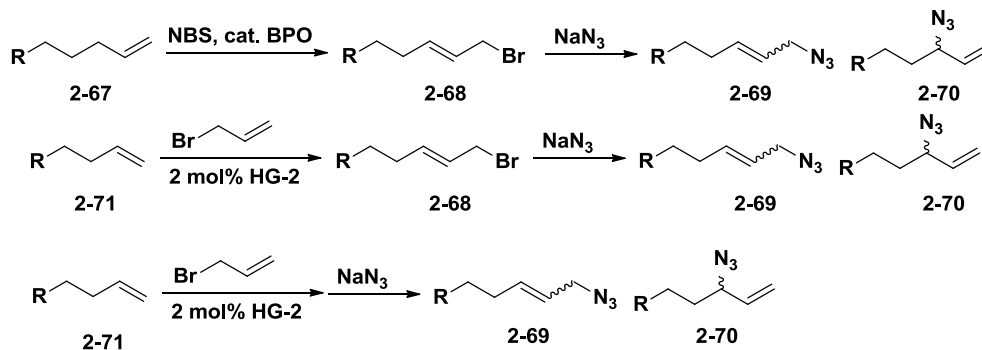


Figure 43. Preparation of allylic azides.

Most olefins were prepared by the alkylation of hydrazone and its subsequent hydrolysis (Figure 44). The hydrazone was quickly accessed by the condensation between ketone and dimethyl hydrazine.

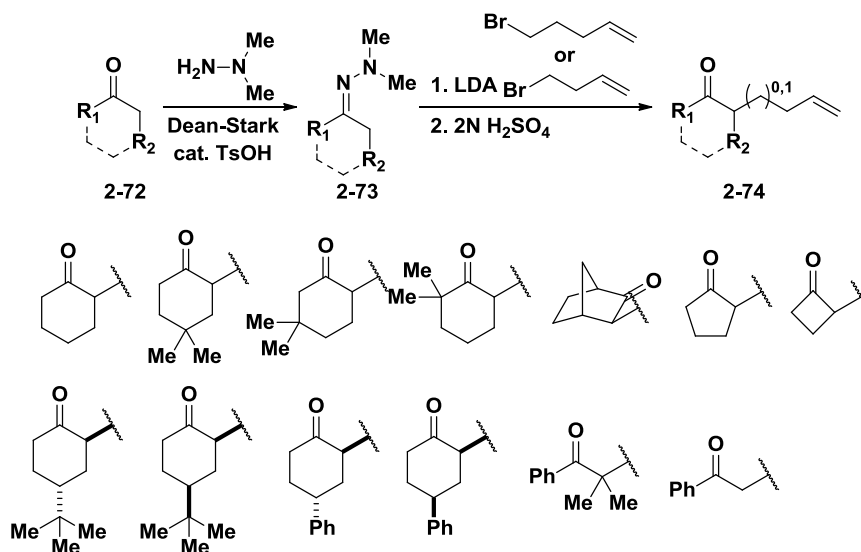


Figure 44. Preparation of olefins.

Some olefins were prepared by the direct alkylation of ketones or Hosomi-Sakurai reaction (Figure 45), and the stereochemistry of one ketone was confirmed by X-ray crystallography (Figure 46).

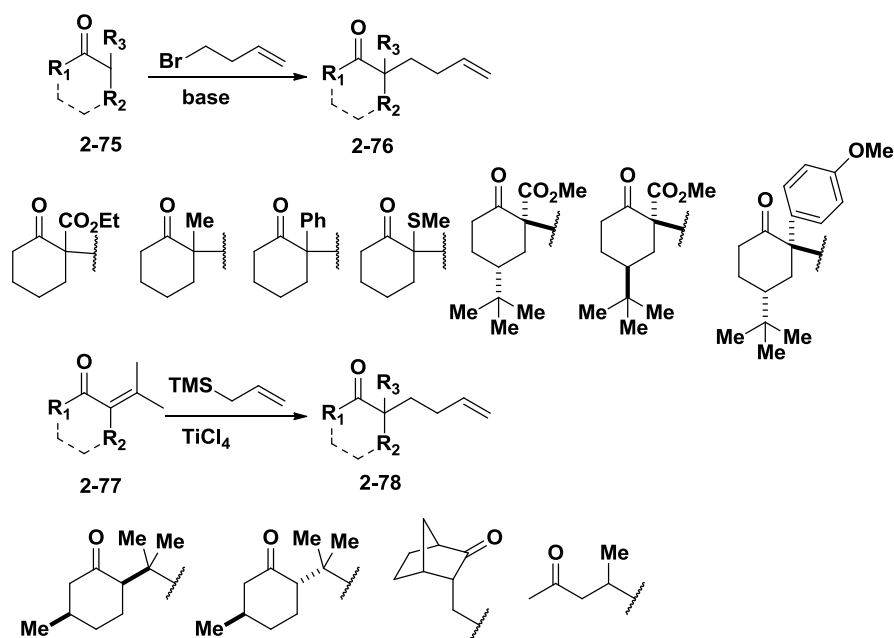


Figure 45. Preparation of olefins using alkylations and conjugate additions.

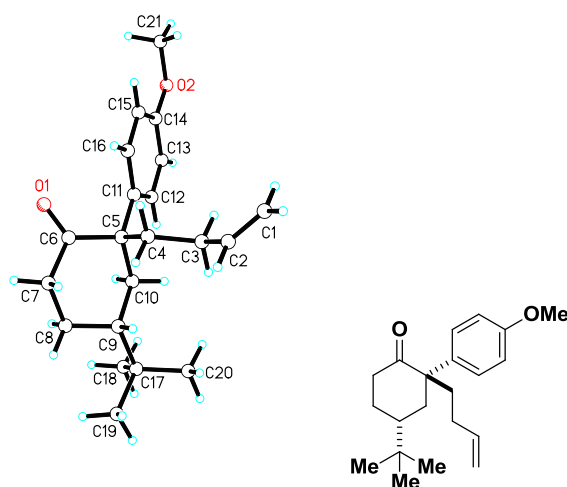
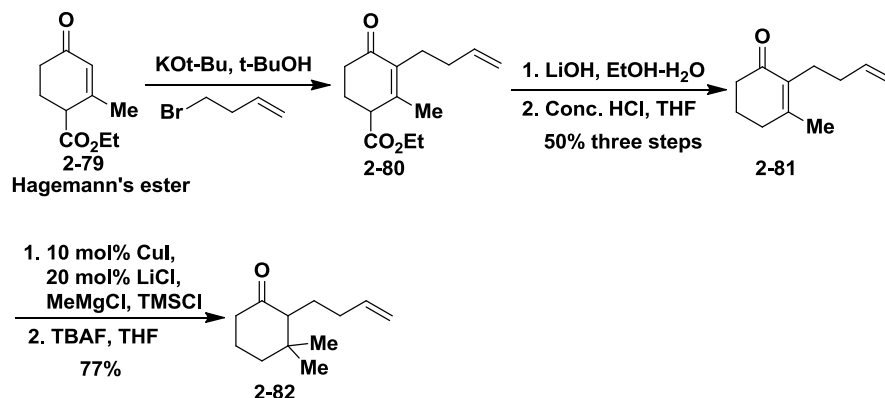


Figure 46. ORTEP representation of (2*S**,4*R**)-2-(but-3-enyl)-4-tert-butyl-2-(4-methoxyphenyl)cyclohexanone.

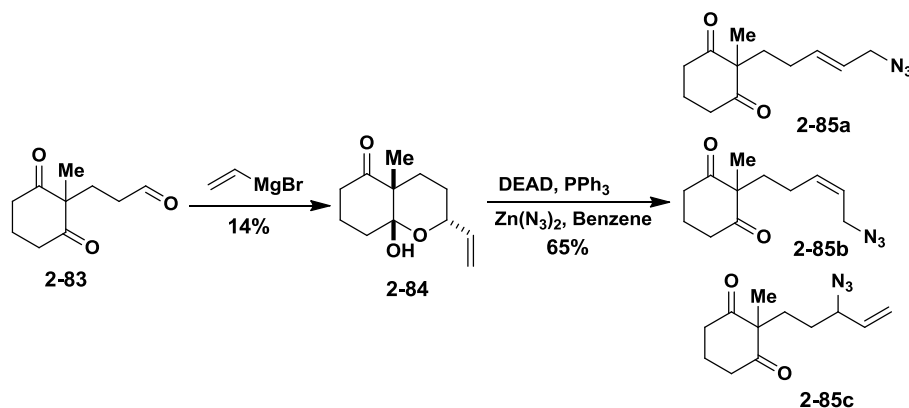
The 3,3-dimethyl cyclohexanone substrate was difficult to prepare. After several failed attempts, it was finally prepared from Hagemann's ester **2-79** (Scheme 58). The first

alkylation occurred at 2 position and the subsequent decarboxylation and conjugate reduction afforded the desired ketone **2-82**.



Scheme 58. Preparation of 3,3-dimethyl-containing substrate.

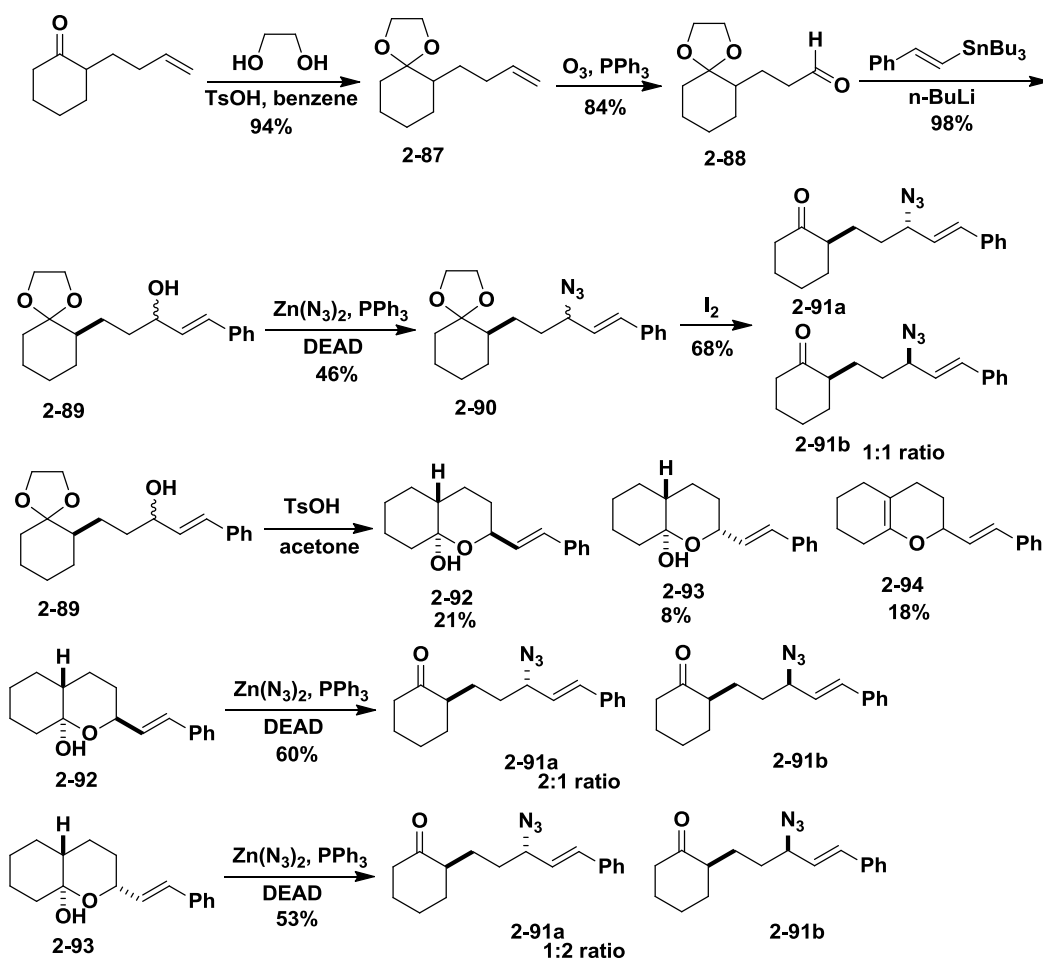
The 1,3-cyclohexandione substrate was prepared from known aldehyde **2-83** (Scheme 59). Due to stronger electrophilicity of aldehyde than ketone, the attack of vinyl Grignard reagent occurred selectively at the carbonyl group of aldehyde. The following Mitsunobu reaction afforded the desired allylic azides **2-85**.



Scheme 59. Preparation of 1,3-diketone substrate.

Phenyl substituted allylic azides **2-91** only have two isomers due to the strongly conjugated styrene system (Scheme 60). 2-(But-3-en-1-yl)cyclohexanone was protected as ketal form **2-87**, followed by oxidation and vinyl attack to afford allylic alcohol **2-89**. Azide

displacement and deprotection provided a mixture of allylic azides **2-91a** and **2-91b** in a 1:1 ratio, whose stereochemistry was arbitrarily assigned. Before the azide displacement, the deprotection gave a separable mixture of three compounds **2-92**, **2-93** and **2-94**. Two of them can be utilized to afford a mixture of allylic azides **2-91** with 2:1 and 1:2 ratios, respectively.



Scheme 60. Preparation of phenyl-substituted allylic azides.

2.4 Allylic azide rearrangement

Introduction. Regarding the transition state of allylic azide rearrangement, Winstein and coworkers stated “the azide isomerization is an instructive example in the whole

spectrum of merging ion pair and non-ionic cyclic rearrangement mechanisms of allylic rearrangement.”⁸⁸ VanderWerf and coworkers described this transition state as “a nearly planar, six-membered ring”.⁸⁹ After that, based on our knowledge, there has been no more discussion until now, except some computational calculations.

In 2004, Saripinar and coworkers reported the rearrangement of cyclic allylic diazide and used PM3 calculation to rationalize why *cis*-1,4-diazidocyclohex-2-ene and *cis*-1,4-diazidocyclohept-2-ene can, *cis*-1,4-diazidocyclopent-2-ene and *cis*-1,4-diazidocyclooct-2-ene cannot, rearrange to their corresponding isomers.⁹⁸ Through the PM3 calculation, they compared several different transition states and found that the energy barrier for an allylic azide is lowest on a six-membered ring. It is only 39.5 kcal/mol for cyclohexene, 46.1 for cycloheptene, 50.2 for cyclopentene, 52.9 for cyclooctene. This explains why cyclopentene and cyclooctene cannot undergo allylic azide rearrangement.

In 2010, Jabbari used CBS-QB3 and density functional studies to explore the [3,3]-sigmatropic rearrangement of allylic azides and found that this reaction is a concerted process that proceeds via a half-chair transition state.⁹⁹ The activation barrier for the simplified allylic azide rearrangement is 20-22 kcal/mol.

Allylic azide rearrangement. As discussed above, allylic azide rearrangement is facile at room temperature due to its low energy barriers. Allylic azides are usually composed of three isomers: *trans*, *cis*, and internal isomers (Figure 47). There is a considerable resemblance between allylic azide rearrangement and ynamide aza-claisen rearrangement. It is highly possible that allylic azide rearrangement undergoes through a six-membered ring with half chair conformation, as computational calculations predicted. In order to interpret this transition state as clear as possible, chair conformation **2-106**, instead of half-chair

conformation **2-105**, is used to resemble the transition state of allylic azide rearrangement in this context.

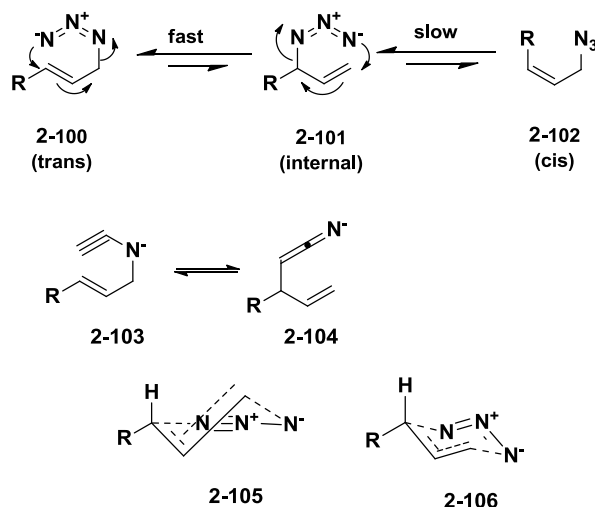


Figure 47. Allylic azide rearrangement and its mechanism.

Herein, the easily understandable chair-conformation is still used to clarify the stereochemistry issue due to its same results as half-chair conformation although chair-conformation is not preferred in the actual allylic rearrangement. If one of the appendages in the isomeric allylic azides has one or two chiral centers, there are two diastereo-differentiated internal isomers **2-107c** and **2-107d** (Figure 48). The change between trans **2-107a** and cis **2-107b** must go through internal isomers **2-107c** and **2-107d** via transition states **2-108** and **2-109**, or **2-110** and **2-111**. Usually, the trans **2-107a** is most stable due to less steric hindrance while the cis isomer **2-107b** is least stable due to $A^{1,3}$ strain. Its reaction coordinate is also shown in Figure 48, in which cis **2-107b** has the highest energy. In some cases, cis isomer **2-107b** is more stable than internal isomers **2-107c** and **2-107d** if the carbon of the alkyl chain next to the allylic azide is quaternary, which is to be discussed later. The steric crowding pushes the azide away from that, thus favoring the stable existence of cis isomer **2-107b**.

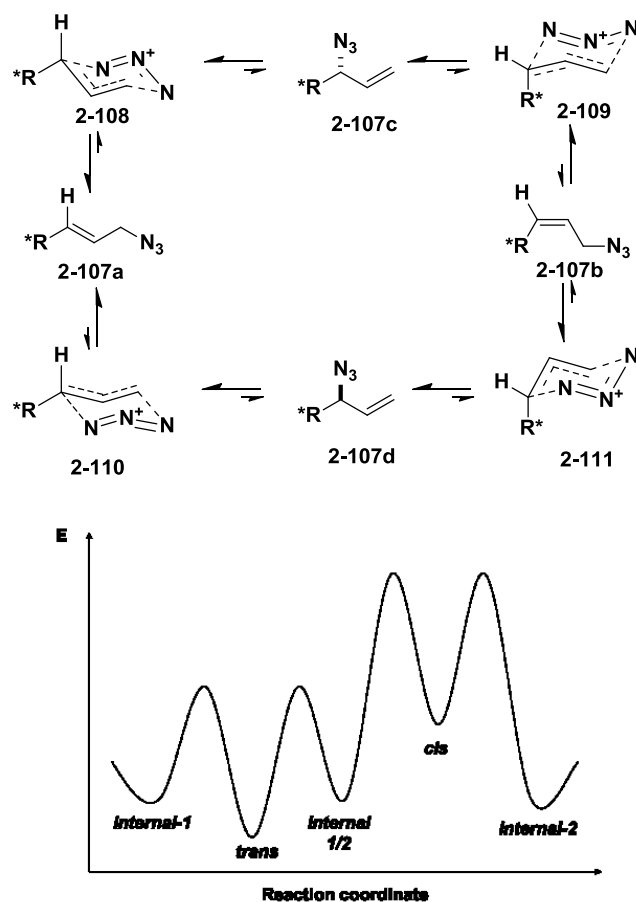


Figure 48. Schematic presentation of allylic azide rearrangement with chiral substituents.

Figure 49 shows the allylic azide rearrangement with two appendages along two sides of the allylic azide. Based on the sigmatropic rearrangement, isomer **2-112a** can be converted to **2-112b** but not to **2-113** with the inverted stereochemistry. This will help us understand why carbocation is involved in this allylic azide rearrangement, which is to be explained later in this chapter.

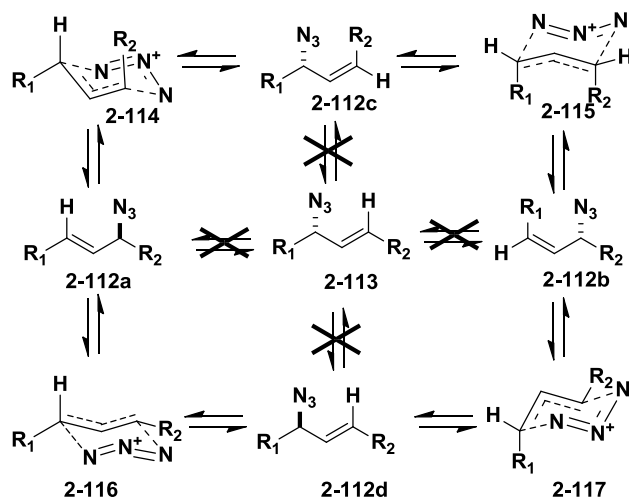


Figure 49. Schematic presentation of allylic azide rearrangement with two substituents.

Spectral data for ratio determination. All the interconvertible isomers of allylic azides are discernible in the proton (^1H) or carbon (^{13}C) NMR spectra using either CDCl_3 or acetone as the solvent (Figure 50). Ha_1 always shows up as a doublet splitting in the ^1H NMR spectrum. In ^1H NMR of the CDCl_3 solution, Hb_1 and Hc_1 usually overlap; however, they are easily recognized in the acetone solution due to doublet splitting for Hb_1 , whose coupling constant is slightly smaller (~ 6.8 Hz) than Ha_1 's (~ 7.2 Hz), and quartet splitting for Hc_1 . In all the ^1H NMR spectra, Ha_3 , Hb_3 and Hc_2 are mixed together, as Ha_2 and Hb_2 are; but Hc_3 are easily identified due to its chemical shift and coupling pattern. So, the rough ratio can be obtained by combining the recognition of Ha_1 , Hb_1 and Hc_1 in the acetone solution. The ratio of a:b:c is equal to $\frac{1}{2}$ integration of Ha_1 : $\frac{1}{2}$ integration of Hb_1 : integration of Hc_1 . In CDCl_3 solution, it should be $\frac{1}{2}$ integration of Ha_1 : $\frac{1}{2}$ [integration of $(\text{Hb}_1 + \text{Hc}_1) - \frac{1}{2}$ integration of Hc_3] : $\frac{1}{2}$ integration of Hc_3 due to the overlapping of Hb_1 and Hc_1 . Both methods give the similar results. In addition, two internal isomers should be considered in the case of chiral

substituents in the molecule. Then the equation should be modified correspondingly to get the ratio of four isomers.

For all the carbon NMR spectra, the combination of ^{13}C and DEPT was utilized to easily recognize carbons Cc_3 and Cc_2 due to their tertiary carbon nature and chemical shift. The comparison between ^1H NMR and ^{13}C NMR can help identify the remaining carbons; in some cases, the integration of ^{13}C peaks is necessary. The rough ratio can be obtained from recognition of Ca_1 , Cb_1 and Cc_1 , or from the integration of carbonyl groups. In most cases, ^1H NMR can not identify the difference between two internal isomers; but the integration of two Cc_2 carbons can tell their differences, although they are same in most cases. Due to a big error margin in the integration of ^{13}C peaks, this method is only recommended as a last resort.

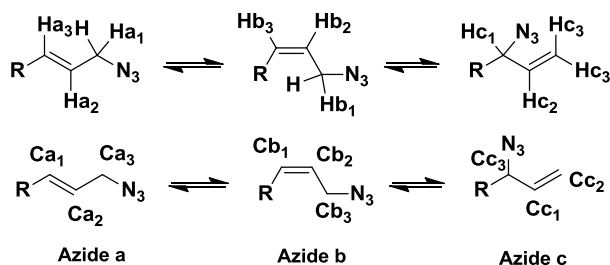


Figure 50. Proton and carbon numbering of allylic azides.

The ^1H NMR spectrum of **2-146** is shown in Figure 51. The ratio of four isomers (a:b:c:d) is 1.0 : 0.1 [$\frac{1}{2} * (0.50 + 0.08 - \frac{1}{2} * 0.77)$] : 0.19 ($\frac{1}{4} * 0.77$) : 0.19, which is converted to 65:7:14:14 in 100% percentage in CDCl_3 , but it is 63:7:15:15 in acetone solution.

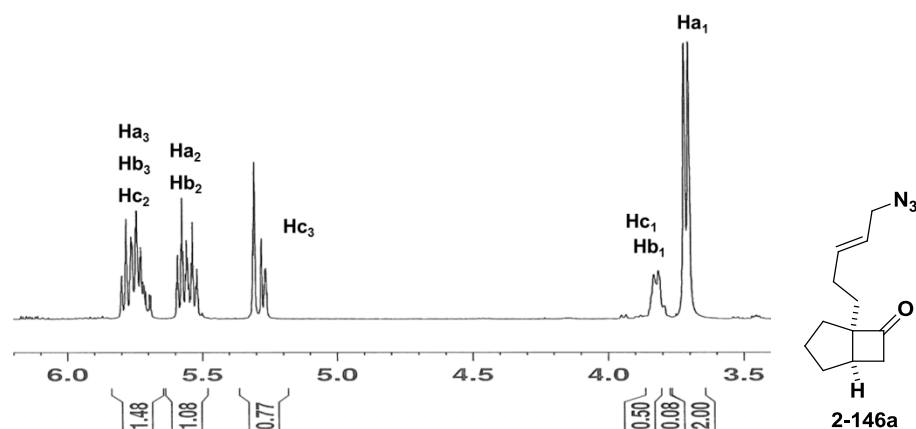
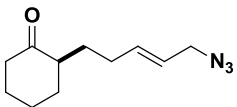
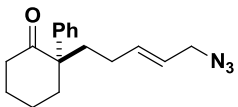
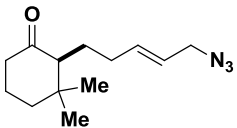
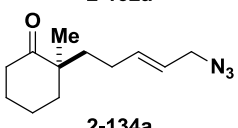
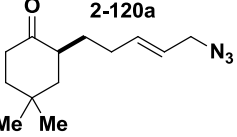
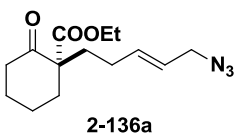
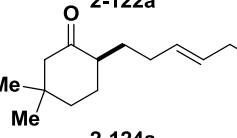
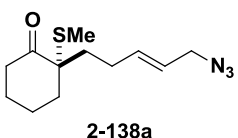
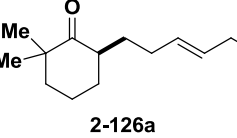
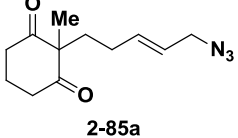
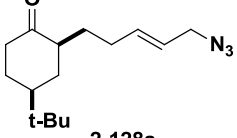
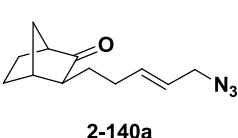
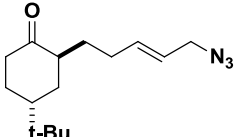
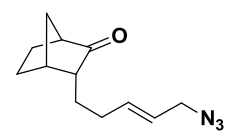


Figure 51. ^1H NMR spectrum for the ratio determination.

All the allylic azides showed very strong stretching absorption at 2100 cm^{-1} in the IR spectra. For HRMS, its exact MS peak is not always shown; sometimes, $2\text{M}-\text{N}_2$ is the major ionization peak.

Substrate-dependent ratio. Most of γ - and δ - substituted allylic azides have a similar pattern of composition, which contains 48–67% of trans isomer, 5–13% of cis isomer, and 24–44% of internal isomer (Figure 52). The effect of solvents in the allylic azide rearrangement is negligible, the ratio difference being under the error margin of determination method. A similar result has been reported by Winstein and coworkers.⁸⁸ Based on the correlation between energy difference and ratio (Table 8), the cis isomer is ~ 1.0 – 1.3 kcal/mol higher than trans isomer, and internal isomer is only ~ 0.2 – 0.5 kcal/mol higher than trans isomer.

Structure (only trans isomer shown)	Ratio (a:b:c:d (if applied))	Structure (only trans isomer shown)	Ratio (a:b:c:d (if applied))
	62:8:15:15 (¹ H, acetone) 64:6:15:15 (¹ H, CDCl ₃)		48:8:22:22 (¹ H, acetone)
2-65a		2-132a	
	67:9:12:12 (¹ H, CDCl ₃)		55:7:19:19 (¹ H, acetone) 55:9:18:18 (¹ H, CDCl ₃)
2-120a		2-134a	
	63:7:15:15 (¹ H, CDCl ₃)		59:7:17:17 (¹ H, acetone) 63:7:15:15 (¹ H, CDCl ₃)
2-122a		2-136a	
	63:7:15:15 (¹ H, acetone)		58:10:16:16 (¹ H, CDCl ₃)
2-124a		2-138a	
	65:5:15:15 (¹ H, acetone)		63:6:31 (¹ H, acetone) 64:6:30 (¹ H, CDCl ₃)
2-126a		2-85a	
	67:7:13:13 (¹ H, acetone) 60:6:17:17 (¹ H, CDCl ₃)		64:8:14:14 (¹ H, acetone) 68:8:12:12 (¹ H, CDCl ₃)
2-128a		2-140a	
	63:9:14:14 (¹ H, acetone)		63:7:15:15 (¹ H, acetone) 68:8:12:12 (¹ H, CDCl ₃)
2-130a		2-142a	

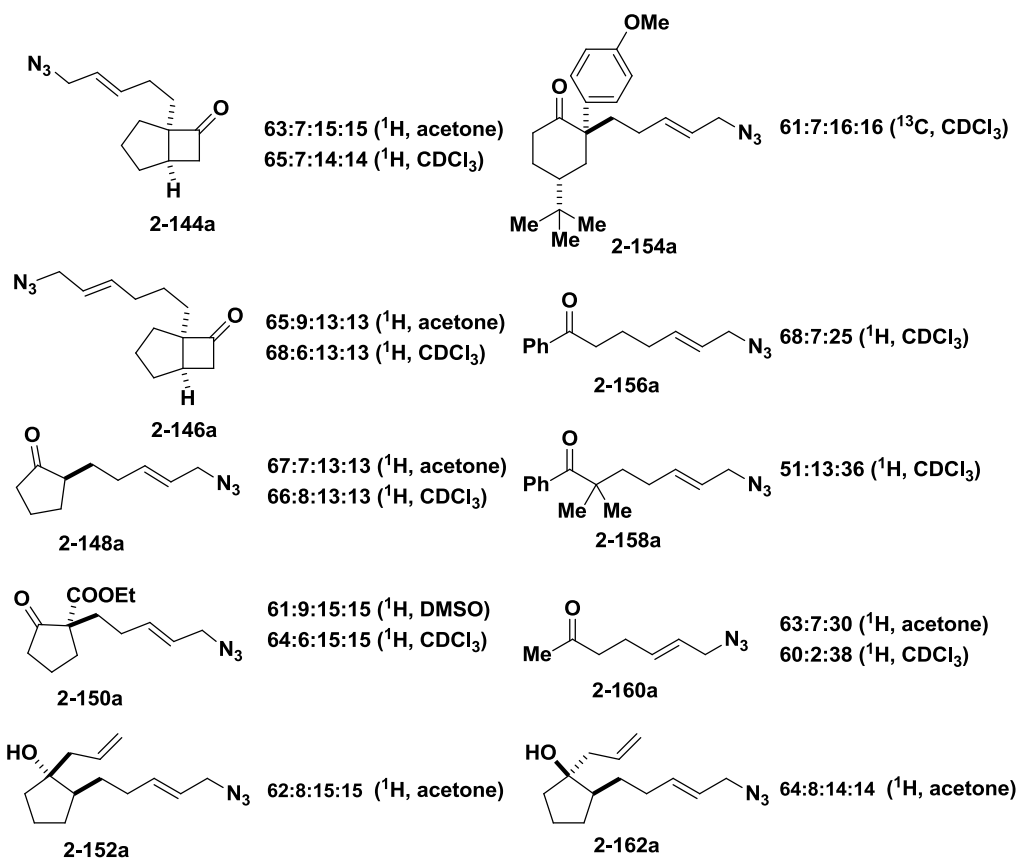


Figure 52. γ- or δ- substituted allylic azides.

Table 8. Correlation between energy difference and ratio.



$$K = e^{-\Delta G^0/RT}$$

Energy difference (kcal/mol)	% more stable isomer	% less stable isomer	K
0	50	50	1
0.119	55	45	1.22

0.239	60	40	1.50
0.365	65	35	1.86
0.501	70	30	2.33
0.649	75	25	3
0.819	80	20	4
1.03	85	15	5.67
1.30	90	10	9
1.74	95	5	19
2.72	99	1	99

For γ - or δ - substituted allylic azides, the substituent has no discernible effect on the equilibration of allylic azides. In the cis isomer, there is a strong repulsive force between Hb₃ and Hb₂. In comparison, the repulsive force between N₃ and Hc₂ is much smaller due to the flexible orientation of N₂⁺ ion. But, it is still bigger than the steric hindrance between Ha₁ and Ha₂. This greatly explains why the internal isomer is ~0.2–0.5 kcal/mol higher and the cis isomer is ~1.0–1.3 kcal/mol higher representively than the trans isomer.

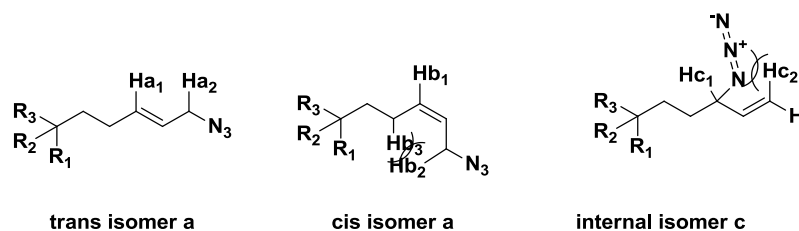


Figure 53. Steric interaction existed in the γ - or δ - substituted allylic azides.

For β -substituted allylic azides, di- and tri-substituted allylic ones have different composition pattern (Figure 54). In comparison to γ -substituted allylic azides, all the β -substituted allylic azides have a smaller population of internal isomers, and tri-substituted

compounds having an even smaller population only up to 3%. The internal isomer of di-substituted allylic azides is 10–18%, which is about half of γ -substituted allylic azides. Cis isomer's population does not have any difference with γ -substituted allylic azides.

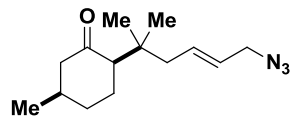
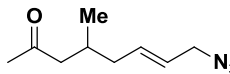
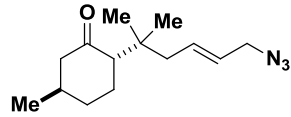
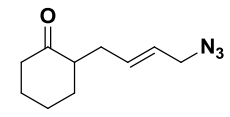
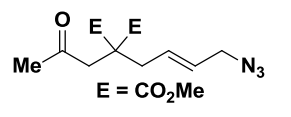
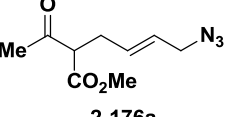
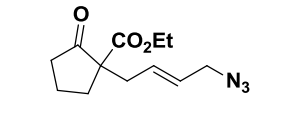
Structure (only trans isomer shown)	Ratio (a:b:c:d (if applied))	Structure (only trans isomer shown)	Ratio (a:b:c:d (if applied))
	94:5:0.5:0.5 (^{13}C , CDCl_3) 94:5:0.5:0.5 (^{13}C , acetone)		79:11:5:5 (^1H , CDCl_3)
2-164a		2-172a	
	89:9:1:1 (^{13}C , CDCl_3) 90:8:1:1 (^{13}C , acetone)		68:14:9:9 (^1H , CDCl_3)
2-166a		2-174a	
	64:36:0 (^1H , CDCl_3)		66:20:7:7 (^1H , CDCl_3)
2-168a		2-176a	
	87:10:1.5:1.5 (^1H , CDCl_3) 92:6:1:1 (^1H , benzene) 92:6:1:1 (^1H , DMSO)		
2-170a			

Figure 54. β -substituted allylic azides.

The steric hindrance of trans and cis isomers for γ - and β -substituted allylic azides is similar (Figure 55). The syn-pentane interaction between R_1 and Ha_1 or Hb_1 confers these molecules higher ground state energy. If $\text{R}_1 \neq \text{H}$, the same interaction between R_1 and N_3 group endows very high energy to the internal isomer. This is why internal isomer's population is so low for the tri-substituted case. For di-substituted case, the interaction is dramatically lessened, although it is still worse than γ -substituted allylic azides.

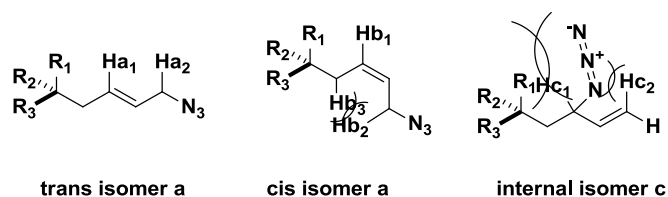


Figure 55. Steric interaction existed in the β - substituted allylic azides.

The interaction pattern of inter-substituted allylic azides changed when a methyl group was added to the middle carbon of the allyl group (Figure 56). Here, the internal isomer became the major isomer, occupying half of the population. The ratio between trans and cis isomers remained constant.

Comparing trans isomer to internal isomer, there is a strong repulsive force between Ha_5 and Ha_4 of trans isomer; However, this interaction is smaller for internal isomer due to the rotating allylic bond. But, the interaction between Hc_2 and N group is bigger than trans isomer. This compromise only makes the internal isomer's population is slightly bigger than that of trans isomer. In addition, the energy difference between trans isomer and cis isomer remained the same.

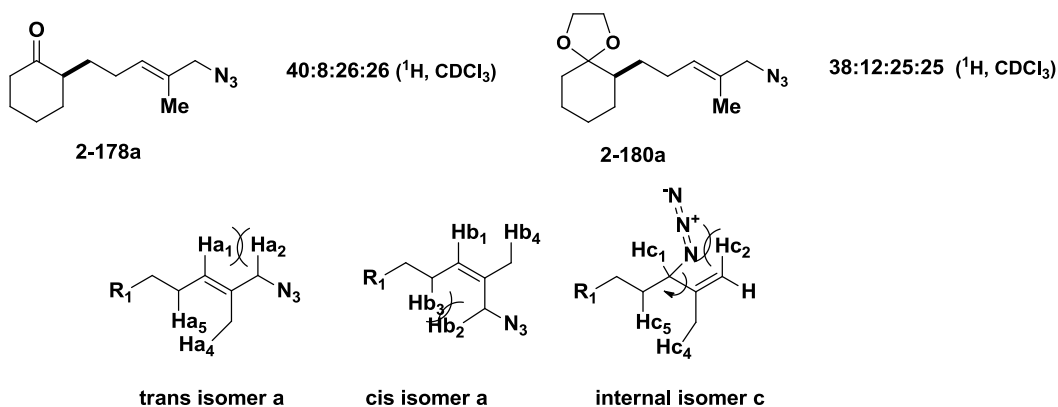


Figure 56. Steric interaction existed in the inter-substituted allylic azides.

Hydroxyl allylic azide rearrangement may be different from those discussed previously due to the existence of H-bonding (Figure 57). For allylic azides **2-181** and **2-185**,

trans isomer and internal isomer have the same percentage, due to 5-membered H-bonding. So the composition pattern is changed for the alkylated allylic azides **2-183** and **2-184**. But, allylic azides **2-182** have a different composition pattern although it has 6-membered H-bonding. It indicated that 6-membered intramolecular H-bonding is relatively weak, and intermolecular H-bonding might be the major contribution here.

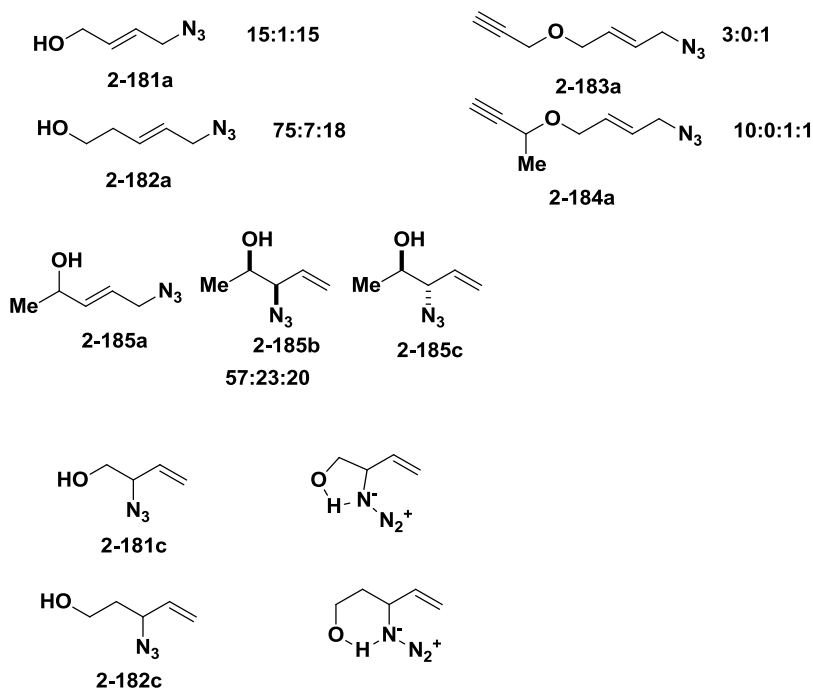


Figure 57. Hydroxyl allylic azide rearrangement.

H-bonding effect also clearly existed for cyclic allylic azides (Figure 58). The large population of **2-186a** over **2-186b** showed that intramolecular H-bonding is relatively strong in comparison with **2-187a** and **2-187b**. Furthermore, conformational analysis indicated that **2-187a** and **2-187b**, both with half-chair conformations, have similar energies. Although the azide group and OR group of **2-187a** have a gauche interaction, it is still slightly more stable than **2-187b**.

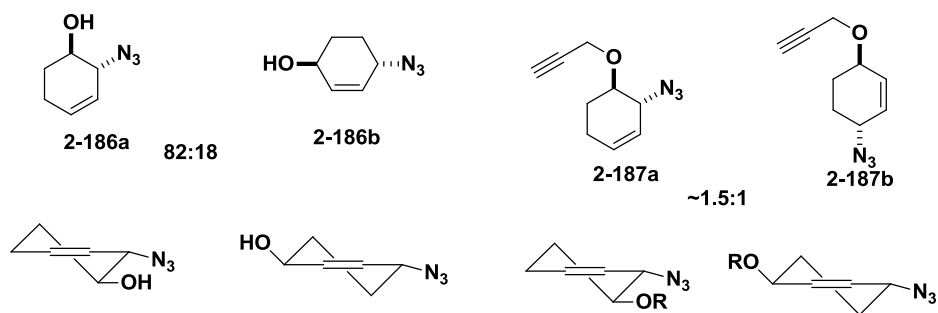


Figure 58. Cyclic allylic azide rearrangement.

For allylic azides **2-188**, $A^{1,3}$ strain results in higher population of trans azide **2-188c** than cis **2-188b** (Figure 59). Currently, it remains unclear why half-chair azide **2-188a** is more stable than chair azide **2-188c** and **2-188b**. But $A^{1,3}$ strain of H_1 and H_2 , lying in the same plane, still could be one of reasons although the molecule with chair conformation is usually ~10 kcal/mol more stable than the one with half-chair conformation.

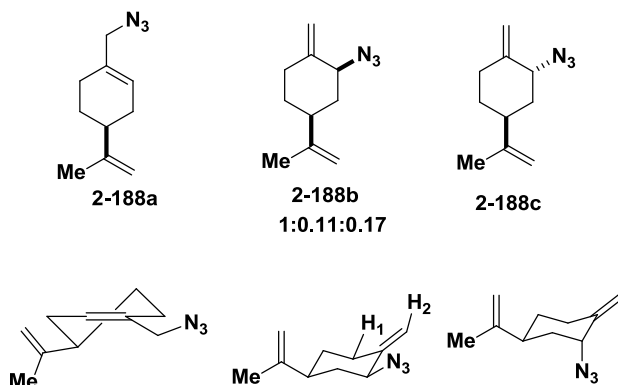


Figure 59. Cyclic allylic azide rearrangement.

Allylic azide is an excellent example to study molecular conformation, because of their interconverting isomers. The higher population of the isomer indicates that the conformation of this isomer is more stable than others.

Time-dependent study. Although allylic azide is an interconverting mixture of three or four isomers, two mixtures, with trans and internal isomers predominant respectively, can be obtained after careful column separation due to their slow interconverting rate. The ratio of

them changes with time until an equilibration is reached. We utilized the NMR technique to track these changes (Figure 60).

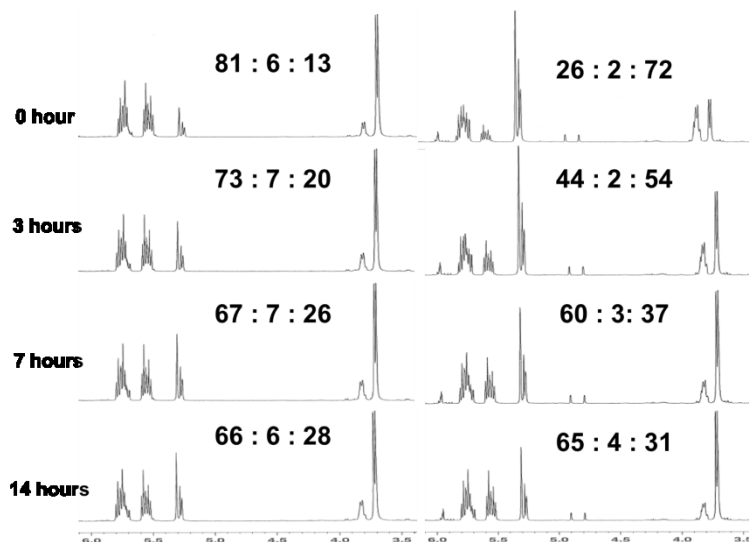


Figure 60. Time-dependent study of allylic azide **2-144**.

The numerical data is shown in Table 9. These data showed that the equilibration was reached after 10–15 h. Theoretically, the k_p/k_s value is equal to **2-144a**/(**2-144c**+**2-144d**): $66/30 = 2.2$. Although there are not enough data, the current data still indicated that k_p is much faster than k_s (Figure 61).

Table 9. Time-dependent study of allylic azides **2-144**.

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> $\text{R}-\text{CH}=\text{CH}-\text{N}_3$ 2-144a </div> <div> $\xrightleftharpoons[k_p]{k_s}$ </div> <div style="text-align: center;"> $\text{R}-\text{CH}(\text{N}_3)-\text{CH}=\text{CH}_2$ 2-144c+2-144d </div> <div> \rightleftharpoons </div> <div style="text-align: center;"> <div style="border: 1px solid black; padding: 2px; display: inline-block;"> $\text{R}-\text{CH}=\text{CH}-\text{N}_3$ </div> 2-144b </div> </div> <div style="margin-left: 20px;"> $\text{R} =$ </div>			
Time	Ratio (a:b:(c+d))	Time	Ratio (a:b:(c+d))
0 h	26:2:72	0 h	81:6:13

3 h	44:2:54	3.5 h	73:7:20
7.5 h	60:3:37	8 h	67:7:26
14.5 h	65:4:31	15 h	66:6:28
19 h	66:4:30	19 h	65:6:29

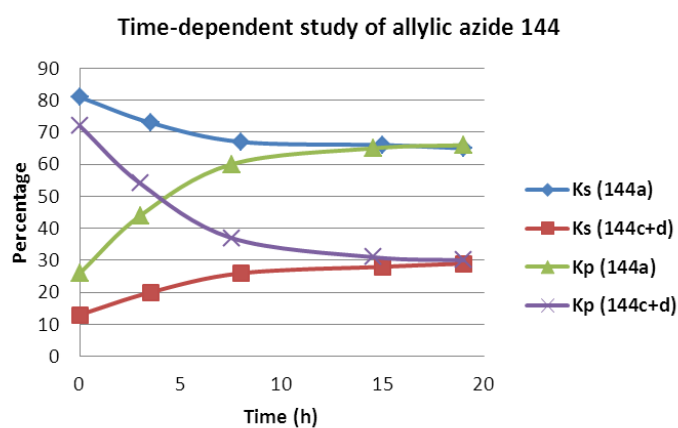
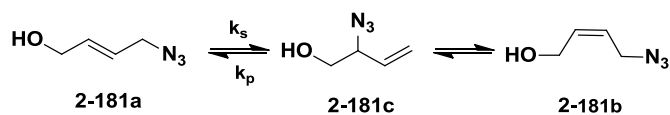


Figure 61. The comparison of k_s and k_p for azides **2-144**.

We also did a time-dependent study with azides **2-181a**, **2-181b**, and **2-181c** (Table 10). Their equilibration was reached after 1–2 days, which indicated their interconverting transition state energy is higher than the one for **2-144**. Its k_p is similar to k_s (Figure 62), which matched their percentage difference (51:48).

Table 10. Time-dependent study of allylic azides **2-181**.



Time	Ratio (a:b:c)	Time	Ratio (a:b:c)
0 min	93:3:4	0 min	7:0:93
84 min	85:3:12	86 min	13:0:87
148 min	82:2:16	151 min	17:0:83
228 min	77:2:21	231 min	22:0:78
276 min	74:2:24	279 min	24:0:76
364 min	70:2:28	365 min	28:0:72
475 min	66:2:32	478 min	32:0:68
589 min	62:2:36	590 min	35:0:65
707 min	60:2:38	709 min	37:0:63
21 h	52:2:46	21 h	43:2:55
27 h	50:2:48	27 h	44:2:54
38 h	49:1:50	38 h	46:2:52
56 h	48:1:51	56 h	47:2:51
23 d	48:1:51	23 d	46:3:51

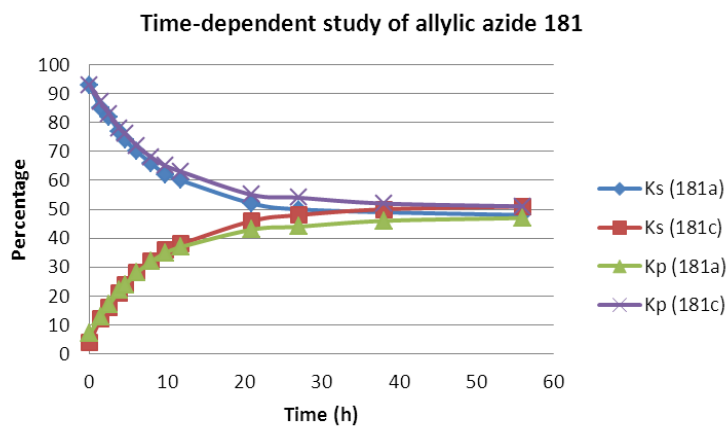


Figure 62. The comparison of k_s and k_p for azides **2-181**.

Isomeric azides **2-182a**, **2-182b** and **2-182c** reached their equilibration in about 10-15 h (Table 11), which is similar to **2-144**. From the initial changes within 4 h, it can be found that k_p is much faster than k_s , which matched with the theoretical k_p/k_s value ($74/18 = 4$) (Figure 63).

Table 11. Time-dependent study of allylic azides **2-182**.

$ \begin{array}{ccccc} \text{HO}-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{N}_3 & \xrightleftharpoons[k_p]{k_s} & \text{HO}-\text{CH}_2-\text{CH}_2-\text{CH}(\text{N}_3)-\text{CH}=\text{CH}_2 & \rightleftharpoons & \text{HO}-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-\text{N}_3 \\ \text{2-182a} & & \text{2-182c} & & \text{2-182b} \end{array} $			
Time	Ratio (a:b:c)	Time	Ratio (a:b:c)
0 h	82:9:9	0 h	3:0:97
2.5 h	78:9:13	2 h	41:1:58

4.5 h	75:9:16	4 h	58:2:40
11.5 h	74:8:18	11 h	72:4:24
20 h	74:8:18	20 h	72:4:24
35 h	74:8:18	35 h	76:5:19
43 h	75:8:17	43 h	76:5:19
68 h	75:8:17	68 h	74:6:20

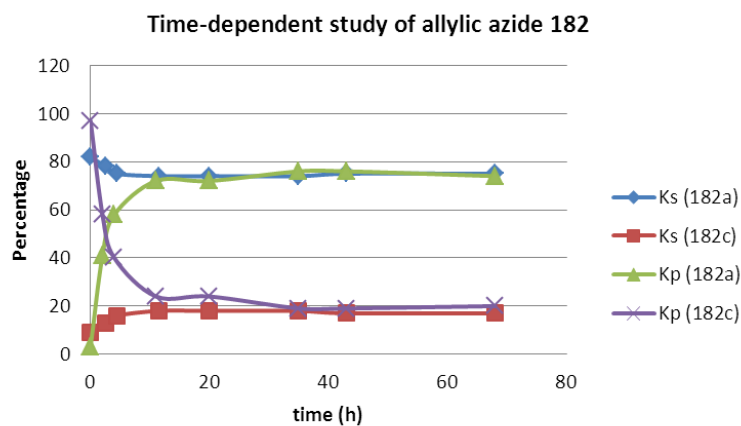


Figure 63. The comparison of k_s and k_p for azides **2-182**.

We also did the time-dependent study of azides **2-186a** and **2-186b** (Table 12). It took about 5–10 days to reach their equilibration (Figure 64), meaning that the energy of their interconverting transition state was relatively high.

Table 12. Time-dependent study of allylic azide **2-186**.

2-186a \rightleftharpoons **2-186b**

Time	Ratio (a:b)	Time	Ratio (a:b)
0 h	100:0	0 h	6:94
15 h	94:6	14 h	30:70
39 h	91:9	38 h	50:50
3.5 d	87:13	3.5 d	67:33
13 d	83:17	13 d	82:18
20 d	83:17	20 d	82:18

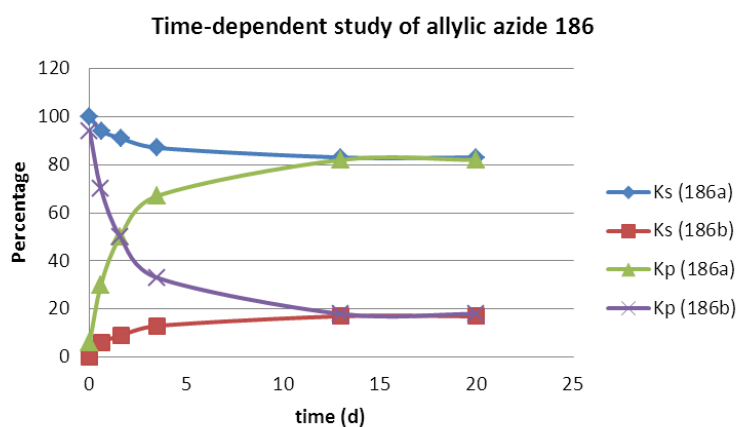
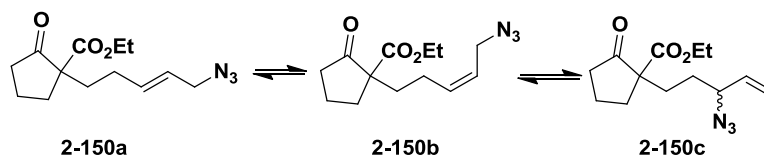


Figure 64. The comparison of k_s and k_p for azides **2-186**.

Variable-temperature experiment. We are also interested at the change of ratio at the difference temperatures. When variable temperature NMR experiments were used to track the change, the ratio was slightly changed at higher temperature (Table 13). The change occurred between trans and cis isomers, while the amount of the internal isomer almost kept constant.

Table 13. Temperature-variable study of allylic azides **2-150**.

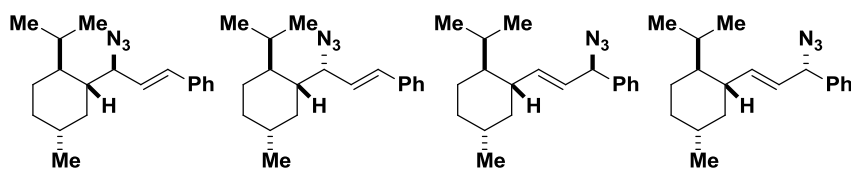


Temperature (°C)	Ratio (a: b: c)
25	70:10:20
55	70:11:19
85	68:14:18
115	66:15:19
135	65:16:19

Following the reported procedure,⁹⁴ allylic azides **2-189** were prepared and variable-temperature experiments were carried out (Table 14). As the temperature increased, the conjugate system of styrene was lost, and the ratio changed from 8.9:1 to 3.0:1. But the ratio went back when the temperature returned to room temperature. It was interesting to find that when the set temperature in the NMR instrument was reached and stabilized, usually taking

several minutes, the equilibration also was also reached. Even though the temperature was kept for 1 h, the ratio did not have a slight variation. It indicated that the equilibrating process was very fast though at the different temperatures.

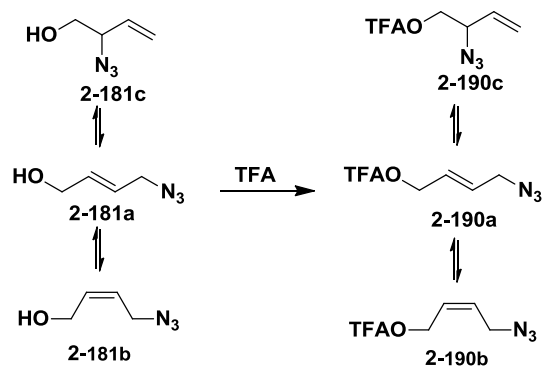
Table 14. Temperature-variable study of allylic azides **2-189**.

			
<div style="display: flex; justify-content: space-around; width: 100%;"> 2-189a 2-189b 2-189c 2-189d </div>			
Temperature (°C)	(2-189a+2-189b):(2-189c+2-189d)	2-189a: 2-189b	
25	8.9 : 1	2.5 : 1	
45	5.9 : 1	nd	
65	4.5 : 1	nd	
85	3.4 : 1	nd	
95	3.2 : 1	nd	
105	3.0 : 1	nd	

Lewis acid-promoted study. Because the combination reaction was to be carried out under the promotion of Lewis acid, we tried to determine if Lewis acid can accelerate the allylic azide rearrangement. We tried several Lewis acids, such as TiCl_4 , SnCl_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$; however, allylic azide was decomposed under these conditions. When allylic azides **2-181** were treated with TFA, acetylated allylic azides **2-190** were obtained. Their time-dependent

variation was recorded (Table 15). The acetylation was not finished even after 2–3 days. It was hard to conclude if TFA promotes this reaction at the current stage.

Table 15. TFA-promoted allylic azide rearrangement.

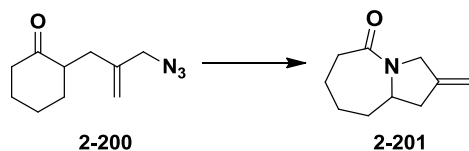


Time	Ratio (2-181c: 2-181a: 2-181b: 2-190c: 2-190a: 2-190b)	Time	Ratio (2-181c: 2-181a: 2-181b: 2-190c: 2-190a: 2-190b)
0 h	45:52:3:0:0:0	0 h	40:57:2:0:1:0
0.15 h	46:51:3:0:0:0	1 h	38:52:2:1:7:0
10 h	38:39:0:4:18:1	9 h	25:31:1:10:32:1
14 h	34:36:0:5:24:1	13 h	21:26:1:13:39:0
25 h	27:30:0:8:35:1	24 h	16:18:1:14:51:0
42 h	21:22:0:11:44:2	42 h	10:13:0:16:62:0
23 d	11:12:0:5:68:4	23 d	6:9:0:10:75:0

2.5 Combined allylic azide rearrangement and intramolecular Schmidt reaction

Initial study. The allylic azide **2-200**, whose 1,3-transposed azide is the same as itself, was first used to know if allylic azides were stable under the necessary Lewis acid conditions per the Schmidt reaction (Table 16). The conversion of azide **2-200** to lactam **2-201** was achieved in two conditions with 82–83% yield.

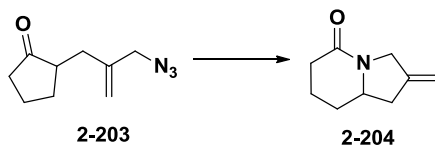
Table 16. The intramolecular Schmidt reaction of allylic azide **2-200**.



Entry	Condition	Yield
1	TFA, rt	82%
2	1.5 eq SnCl ₄ , DCM, reflux	83%

When azide **2-203** was treated with the same conditions, the yield obtained was only 20–24%. The low yielding may be resulted from the torsional strain of five-membered cyclopentanone.

Table 17. The intramolecular Schmidt reaction of allylic azide **2-203**.



Entry	Condition	Yield
1	TFA, rt	20%
2	1.5 eq SnCl ₄ , DCM, reflux	24%

Condition-screening. Based on our hypothesis shown in Figure 42 and the successful initial studies, a high diastereoselectivity was expected for the combination of allylic azide rearrangement and intramolecular Schmidt reaction.

Various conditions were tested for this combination (Table 18). The best result was obtained with 1.5 eq of tin chloride in refluxing dichloroethane to afford amides **2-66a** and **2-66b** in 68% yield. However, only 1.2:1 ratio was obtained, which was below our expectations. Beside the traditional amides, alcohols **2-66f** and **2-66g** were also obtained with 1.3:0.5 ratio when allylic azide was treated with titanium chloride.

Table 18. Condition-screening for the combination of allylic azides **2-65**.

Entry	Condition	Ratio (2-66a : 2-66b)	Yield (2-66a + 2-66b)	Yield (2-66f + 2-66g)
-------	-----------	--	---	--

1	1.2 eq TiCl ₄ , DCM, rt	1.1:1		16%
2	1.5 eq TiCl ₄ , DCM, rt	1.1:1	23%	(1.3:0.5)
3	1.5 eq SnCl ₄ , DCM, rt	1.1:1	55%	
4	1.5 eq BF ₃ ·OEt ₂ , DCM, rt	1:1	34%	
5	TFA, DCM, rt	1:1	34%	

6	1.5 eq SnCl ₄ , DCM, 0 °C	1.1:1	36%
7	1.5 eq SnCl ₄ , DCM, reflux	1.2:1	60%
8	1.5 eq SnCl ₄ , DCE, reflux	1.3:1	54%
9	1.5 eq SnCl ₄ , DCM, rt	1.2:1	56%
10	1.5 eq SnCl ₄ , DCM, reflux	1.2:1	66%
	(500 mg scale-up)		(68%)
11	3 eq TMSOTf, DCM, rt	1:1	28%
12	3 eq MeAlCl ₂ , DCM rt	2.4:1	21%

Mechanistic analysis. Based on the mechanistic study in the traditional intramolecular Schmidt reaction shown in Figure 36, there are two reactive conformers *eq-2-65d* and *ax-2-65d* for cyclohexanone substituted allylic azide **2-65d** (Figure 65). For equatorial conformer *eq-2-65d*, azide can possibly attack the carbonyl group from axial and equatorial positions to produce **2-205** and **2-206**, respectively. Both intermediates lead to the formation of the same lactam **2-66b**. However, for axial conformer *ax-2-65d*, two intermediates **2-207** and **2-208** can be formed due to the orientation of N₂⁺ group, although azide can only attack the carbonyl from the equatorial position. Azidohydrin **2-207** can lead to the formation of lactam **2-66b**; and **2-208** to the formation of twisted amide **2-66e**.

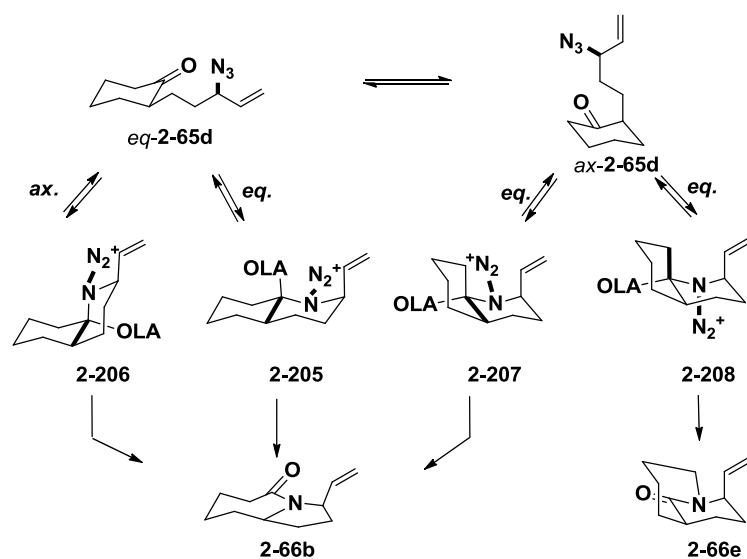


Figure 65. Proposed mechanism for the synthesis of **2-66b**.

The same analysis was applied to azide **2-65c**, where four intermediates **2-209**, **2-210**, **2-211**, and **2-212** can lead to the formation of normal amide **2-66a** and twisted amide **2-66d**, respectively (Figure 66).

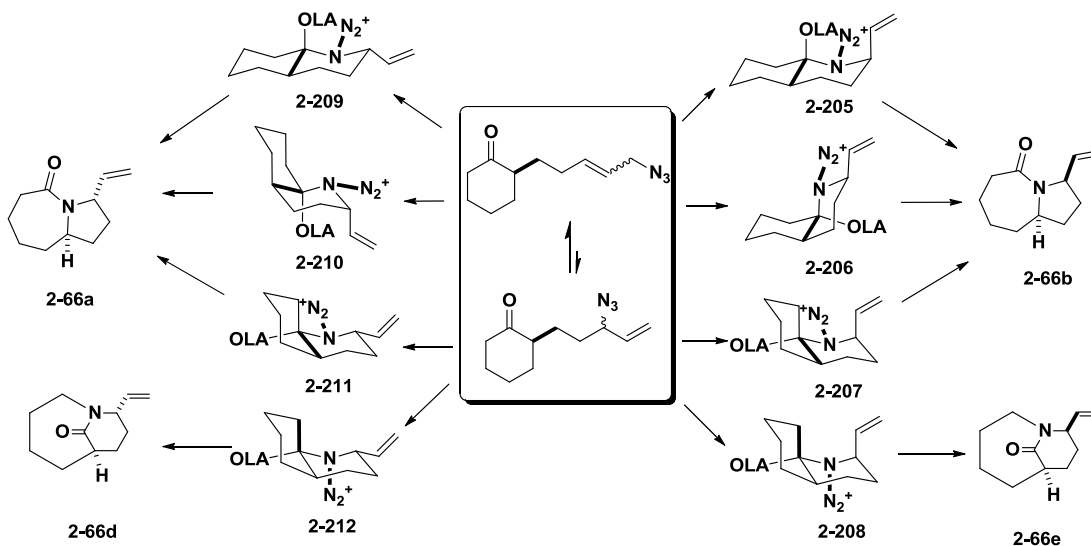


Figure 66. Mechanistic analysis for the combination.

Conformational analysis. Based on the Curtin-Hammett principle, the ratio of products is determined by the relative heights of the highest energy barriers leading to the

products. Because the intramolecular Schmidt reaction is strongly exothermic, the transition state is very close to azidohydrin intermediate (early transition state). We could have a basic image how this reaction goes by analyzing all the azidohydrin intermediates. All the intermediates were compared to find that azidohydrins **2-209** and **2-206** are the major contributors for the production of lactams **2-66a** and **2-66b** due to less steric interactions. Because both vinyl groups are in the equatorial positions, the major difference between both intermediates is the switched azidohydrin center, one of which is with axial OLA group and the other with equatorial OLA group.

Before further conformational analysis, basic knowledge of stereochemistry was summarized in Figure 67. *cis*-Decalin has three butane-gauche interactions and is 2.7 kcal/mol higher in energy than *trans*-decalin.¹⁰⁰ So, butane-gauche interaction in the decalin system is around 0.9 kcal/mol. Depending on the method, *cis*-decalin **2-213** is only 0.55 or 1.39 kcal/mol higher, than *trans*-decalin **2-214** or **2-215** if a methyl group was put on the bridgehead carbon of decalin system.¹⁰⁰ *cis*-Decalin **2-213** has four Me-H synaxial interactions, which are equal to 3.4 kcal/mol if A value of methyl group is 1.7 kcal/mol (equal to two synaxial interactions); *trans*-decalin **2-214** has two Me-H synaxial interactions and three butane-gauche interactions totaling to 4.4 kcal/mol ($1.7 + (3 \times 0.9) = 4.4$). This means that **2-214** is 1 kcal/mol higher than **2-213**, which matches with the experimental result. If nitrogen replaced one of carbons near to bridgehead carbon, **2-216** and **2-217** become different compounds, unlike **2-214** and **2-215**, which have the enantiomeric relationship. The 9:1 ratio of **2-216** and **2-217** indicated that their energy difference is 1.30 kcal/mol.¹⁰⁰ Compound **2-216** has one butane-gauche interaction and two propylamine interactions; and **2-217** has three butane-gauche interactions. So we can induce that the propylamine interaction is around 0.25 kcal/mol ($(3 \times 0.9 - 1.3 - 0.9) / 2 = 0.25$). The low interaction energy of propylamine

interaction is due to the small interaction between lone pair electron of nitrogen and hydrogen atom (Figure 68). The energy difference of **2-218** and **2-219** is not found yet.

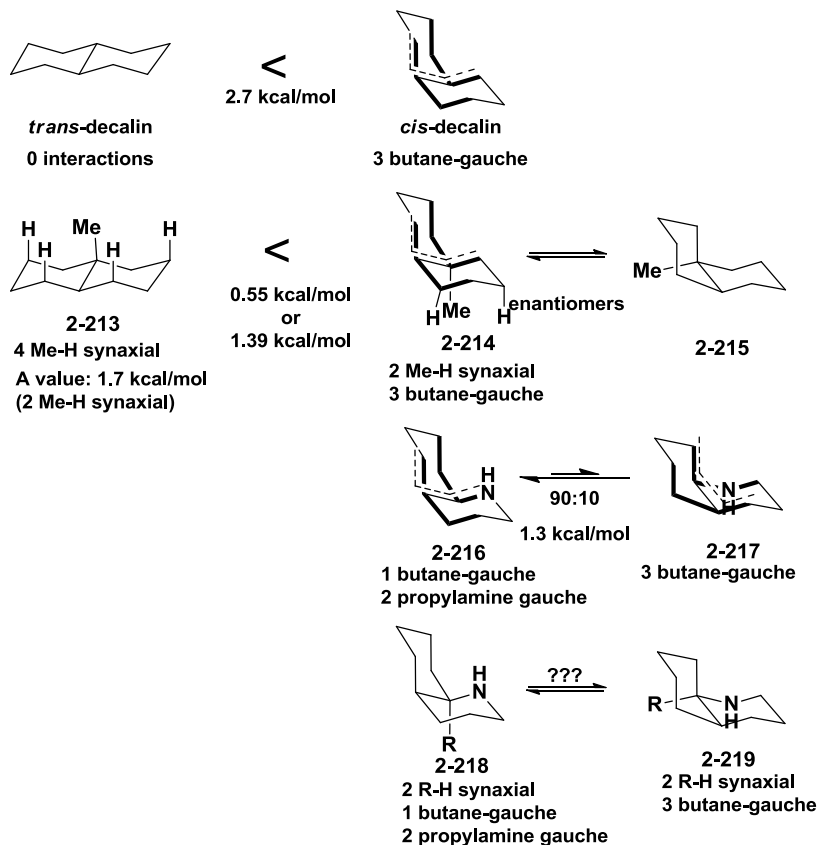


Figure 67. Steric interactions in the decalin system.

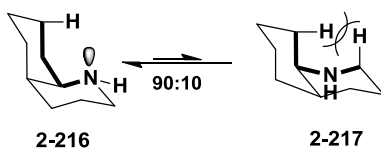


Figure 68. Steric interaction of **2-216** and **2-217**.

With the basic knowledge of stereochemistry in mind, the energies of **2-209** and **2-206** were compared. Intermediate **2-209** has four OLA-H synaxial interactions, and **2-206** has two OLA-H interactions, one butane-gauche interaction and two propylamine-gauche interactions. Here the propylamine interaction with attached N_2^+ group, may be different from

2-218; and it may be little higher than 0.25 kcal/mol. The difference of **2-209** and **2-206** is if two OLA-H interactions (A value of OLA group) compete with one butane-gauche and two propylamine-gauche interactions ($0.9 + 2 \times 0.25 = 1.4$ kcal/mol). If OH (1 kcal/mol) was used to replace OLA group here, **2-209** is about 0.4 kcal/mol more stable than **2-206**. Because the OLA group is bigger than OH group, this greatly matched with the result of 1.2:1 diastereoselectivity.

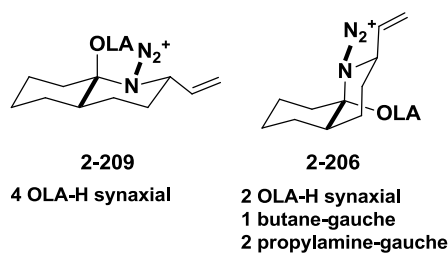


Figure 69. The most stable intermediate in the combination.

Computational calculation. Computational calculation could assist our deeper understanding of the mechanism. Osvaldo Gutierrez and Prof. Dean J. Tantillo from University of California–Davis conducted the computational calculations for us (Figure 70).

All stationary points were calculated using B3LYP with the 6-31G(d,p) basis set (SDD was used for Sn) in DCE (CPCM; UA0) as implemented in GAUSSIAN09. As shown in Figure 70, the relative energies show that all transition states with an axial vinyl group are 5-8 kcal/mol higher in energy than the corresponding transition states with an equatorial vinyl group. Although the vinyl group has an A value around 1.6-2 kcal/mol, the much larger energy difference is attributed to butane-gauche interaction. Therefore, fused lactam **2-66a** arises predominately from **2-209**, although **2-211** certainly contributes, and **2-66b** arises from **2-206**. For this system, the transition state leading to the bridged lactam is too high in energy and is not expected to produce any significant product. Furthermore, the overall barrier from the lowest energy reactant (complexed to SnCl_3) to the lowest energy transition state structure

2-209 is 28.7 kcal/mol, which is much higher than that calculated for the allylic azide rearrangement (ca. 22 kcal/mol) and therefore the overall regio- and diastereoselectivity is controlled by the alkyl migration/ N_2 loss transition state structures.

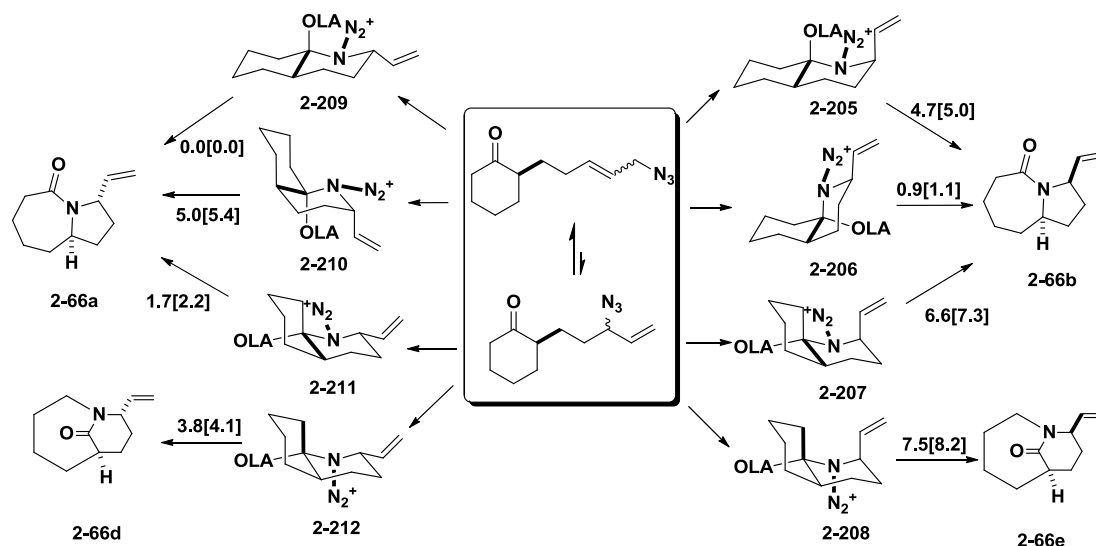


Figure 70. Relative enthalpies (free energies in brackets; 298.15 K) of transition state structures calculated using B3LYP/6-31G(d,p)-[SDD for Sn] in DCE (CPCM;UA0).

Based on the above data, a reaction coordinate diagram can be generated (Figure 71). Based on the Curtin-Hammett principle, the ratio of products **2-66a** and **2-66b** is determined by the difference of the highest energy barriers leading to the products, which are the transition states from **2-209** to **2-66a**, or from **2-206** to **2-66b**. The energy of transition state in the allylic azide rearrangement is relatively lower than that.

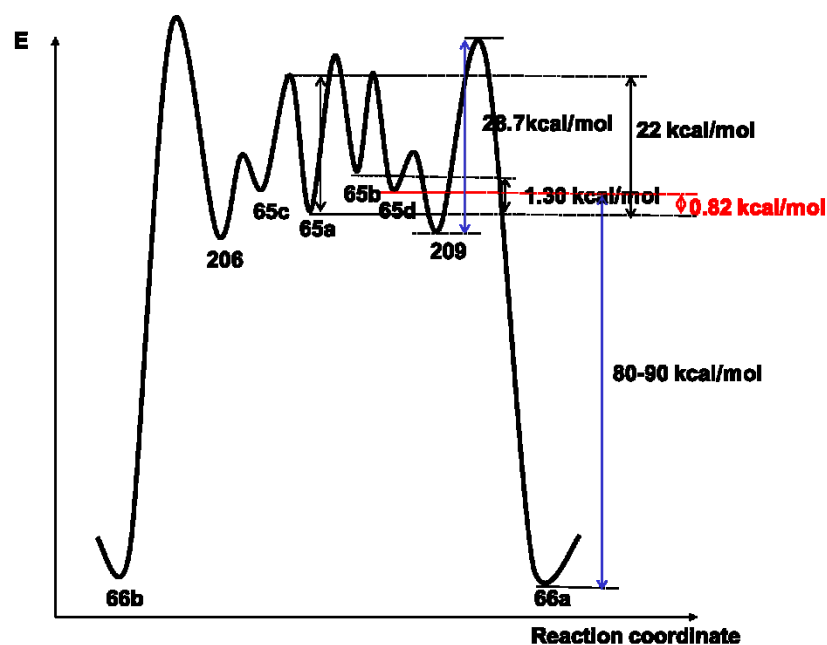
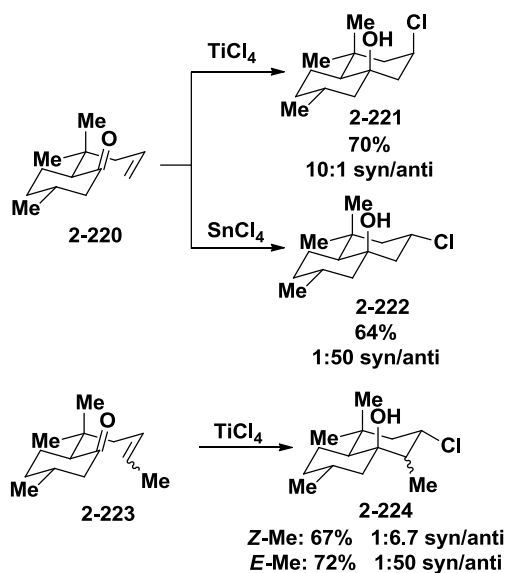


Figure 71. Reaction coordinate diagram of this combination.

Halo-Prins reaction. Coates and coworkers reported the halo-Prins cyclizations of δ -unsaturated ketones to synthesize 1,3-halo hydrins (Scheme 61).^{101,102} Under the promotion of TiCl_4 , a high selectivity for syn products was obtained. However, when SnCl_4 was used, anti-product with high selectivity was obtained. However, with Me-substituted olefin, anti-product is a major product although TiCl_4 was used to promote this reaction.



Scheme 61. Selective halo-Prins reaction.

They also proposed a mechanism to explain the competition between syn- and anti-selective reactions for the halo-Prins cyclization (Figure 72). For syn-selectivity, the chloride from titanium chloride intramolecularly attacked the carbocation **2-226**, generated from the Prins reaction of olefin **2-225**, to produce syn-product **2-230**. The anti-product **2-228** was formed from the corresponding intermolecular attack. The preference of syn-addition product by TiCl_4 was explained by its strong Lewis acidity. The relatively weaker Lewis acid, SnCl_4 , results in slow rate of ion pair collapse to syn-product, and then favors the formation of trans-product.

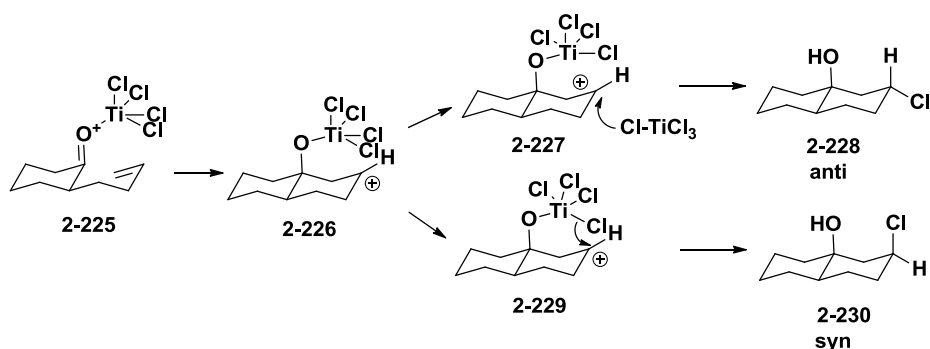


Figure 72. Proposed mechanism for competing syn- and anti-selective halo-Prins cyclizations.

With this in mind, a chloro-Prins reaction can in principle occur in the combination of allylic azide rearrangement and intramolecular Schmidt reaction (Figure 73). These products have been observed in a limited number of cases.

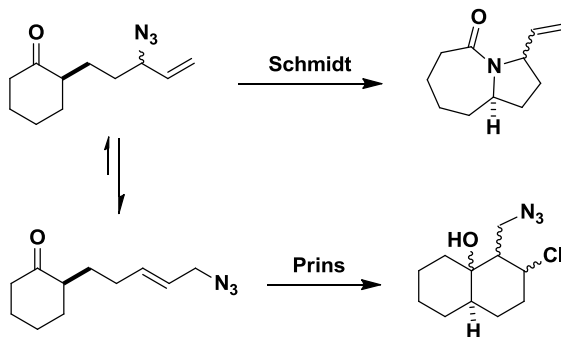


Figure 73. Competitions between Schmidt and Prins reactions.

Based on the mechanistic analysis, five stereoisomers are possible halo-Prins adducts (Figure 74). As mentioned above, carbocation **2-231**, generated from *eq*-attack of **eq-2-65a**, can make ion pair association intramolecularly or intermolecularly to give **2-66f** and **2-66g**, respectively. The same sequence can occur for *ax*-attack of **eq-2-65a** to afford **2-66h** and **2-66i**, respectively. For **ax-2-65a**, there is only one product **2-66j** from the intermolecular ion pair association. When allylic azides **2-65** were treated with TiCl_4 , a mixture of **2-66f** and **2-66g** was obtained in a 16% yield with 1.3:0.5 ratio (entry 2 in Table 18). Their relative stereochemistry was determined by the combination of 2D NMR and coupling patterns. The

diagnostic peaks are the hydrogen atoms marked in green, one with td pattern and the other with q pattern (Figure 74).

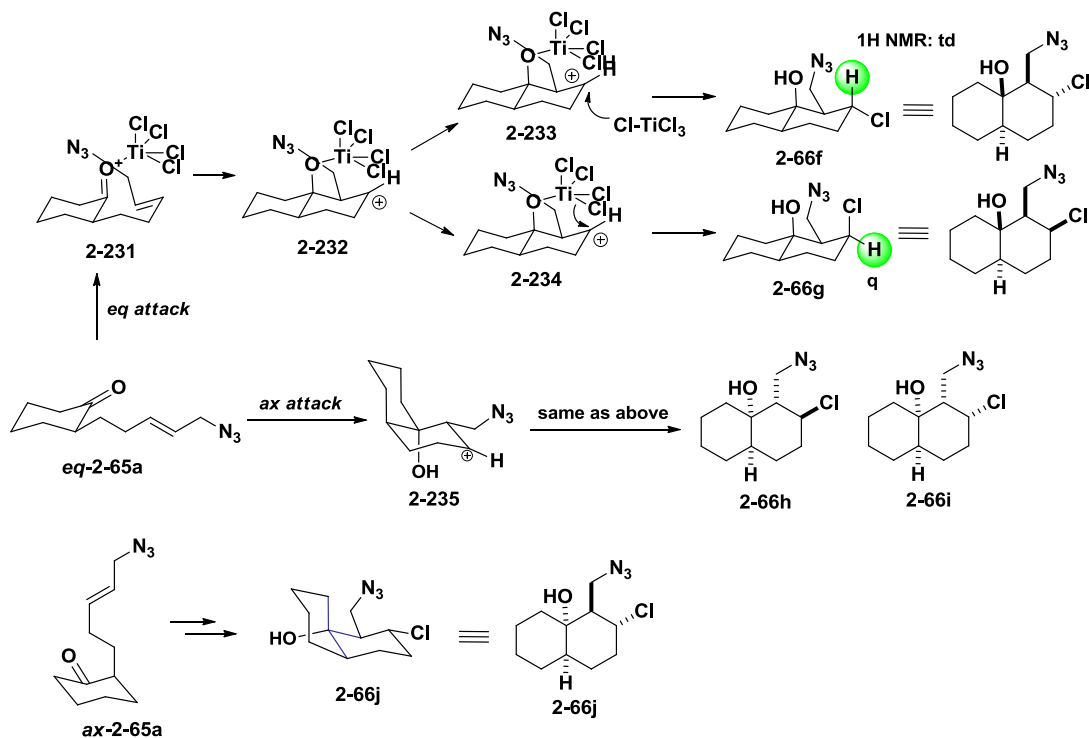


Figure 74. Chloro-Prins reaction of allylic azides.

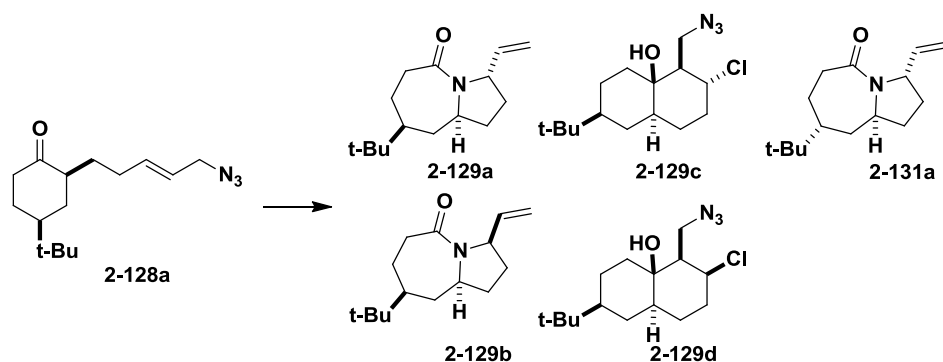
2.6 Stereocontrol in the combination of allylic azide rearrangement and intramolecular Schmidt reaction

In this section, the influence of substituents in the ketone on the diastereoselectivity is to be discussed. In this section and the rest of this chapter, only trans isomer of isomeric allylic azides is shown to represent the whole allylic azides mixture and the term, allylic azides **XXX**, was used to refer a mixture of azides **XXXa**, **XXXb**, **XXXc**, and **XXXd**.

4-*tert*-Butylcyclohexanone is an extreme type of cyclohexanone. The existence of bulky *tert*-butyl group, which is always at the equatorial position, can force the 2-alkyl chain to either equatorial or axial position. *cis*-Allylic azides **2-128** were treated with SnCl_4 to give

lactams **2-129a** and **2-129b** in a 68% yield with 3:1 ratio (Table 19). The ratio was slightly higher than lactam **2-66**'s (1.2:1), which may result from no contribution of intermediate **2-237** (Figure 75). Furthermore, trace amount of lactam **2-131a** was obtained, which may be resulted from the α -center epimerization of ketone **2-128** to **2-130**. The Prins reaction is to be discussed in a separate section and this is also applied for the next examples.

Table 19. Condition-screening for allylic azides **2-128**.



Entry	Condition	Ratio	Yield (2-129a + 2-129b)	Yield (2-129c + 2-129d)
		(2-129a : 2-129b : 2-129c : 2-129d : 2-131a)		
1	1.5 eq SnCl ₄ , DCM, reflux	10:3:0:0:0	63%	
2	1.5 eq SnCl ₄ , DCM, reflux	3:1:0:0:0.05	68%	
3	1.5 eq TiCl ₄ , DCM, rt	0.66:0.6:1.0:0.35:0	34%	24%
4	1.5 eq TiCl ₄ , DCM, rt; M.S.	0.72:0.55:1.0:0.4:0.17	34%	34%
5	10 eq amberlyst 15, DCM, reflux, 3 days	1.8:1:0:0:0.2	68%	
6	1.5 eq SnCl ₄ , DCM, reflux; M. S.	4:1:0.05:0:0:2.2(SM)	45%	

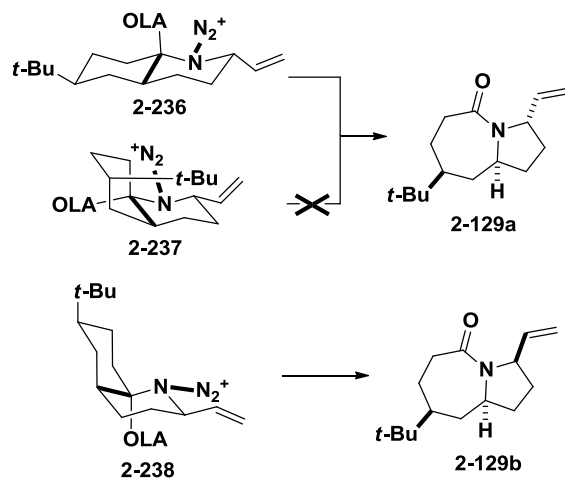
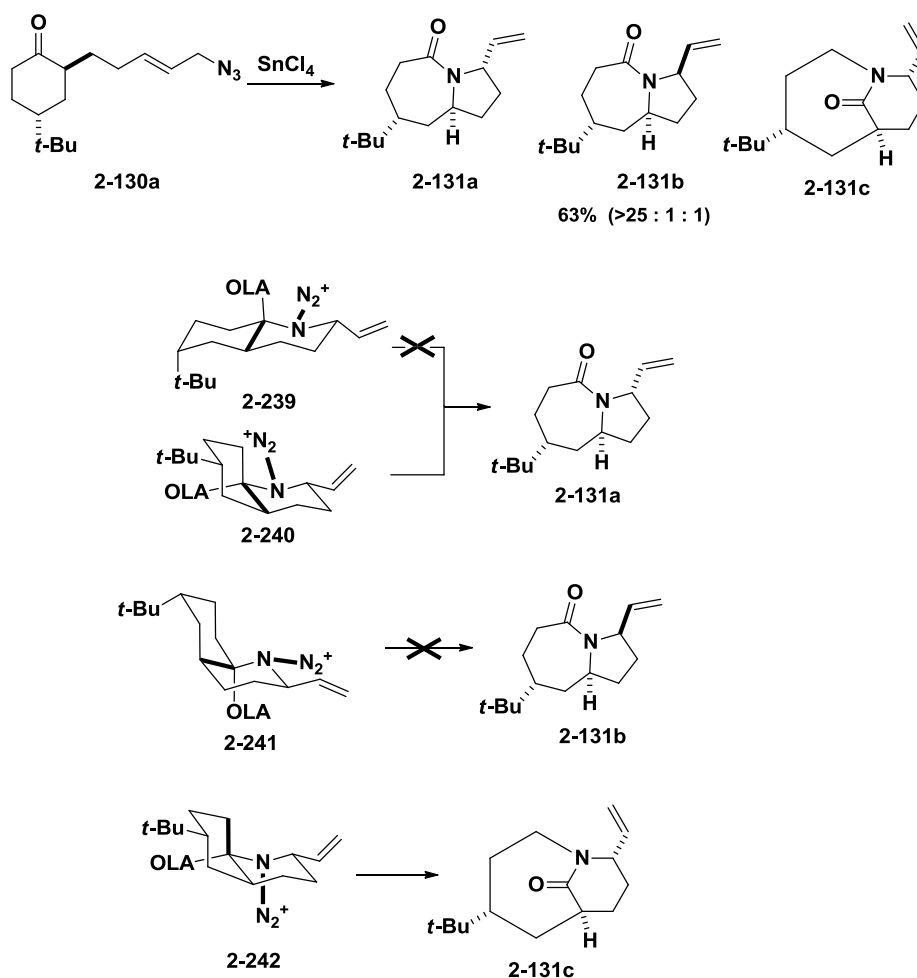


Figure 75. Proposed intermediates to **2-129a** and **2-129b**.

When azide **2-130** was treated with SnCl_4 , lactam **2-131a** was obtained, along with **2-131b** and **2-131c**, in a 63% yield with >25:1:1 ratio (Scheme 62). The instability of intermediate **2-241** due to the axial *tert*-butyl group is the reason high selectivity was obtained. For the production of **2-131a**, most contributions are from intermediate **2-240**, instead of **2-239**. Trace amount of twisted amide **2-131c** was obtained due to the axial orientation of N_2^+ group.



Scheme 62. Generation of lactam **2-129**.

After the understanding of *tert*-butyl group's impact on the diastereoselectivity, we tried to understand the impact of other substituents around the six-membered ring on the diastereoselectivity. The 4,4-Dimethyl substituted cyclohexanone was tested for this combination (Table 20). A similar selectivity (1.6:1~1.7:1) to unsubstituted cyclohexanone was obtained in modest yield (Figure 76).

Table 20. Condition-screening for allylic azides **2-122**.

Entry	Condition	Ratio	Yield
		(2-123a : 2-123b)	(2-123a + 2-123b)
1	1.5 eq SnCl ₄ , DCM, reflux	1.7:1	74%
2	1.5 eq SnCl ₄ , DCM, reflux	1.7:1	66%
3	1.5 eq TiCl ₄ , DCE, reflux	1.6:1	64%

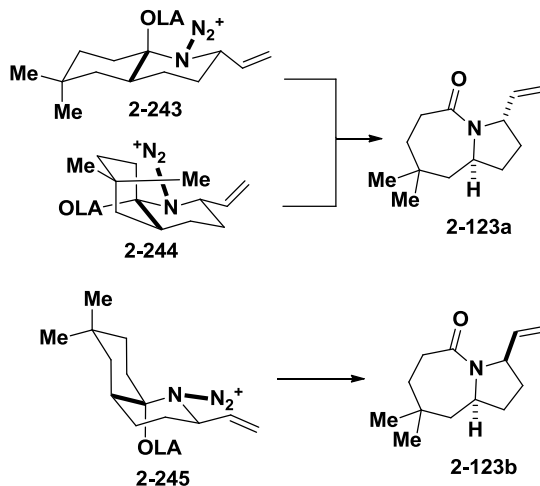


Figure 76. Proposed intermediates to **2-123a** and **2-123b**.

Unfortunately, tin chloride did not work for the transformation from allylic azides **2-126** to lactams **2-127a** and **2-127b** (Table 21). Titanium chloride afforded the desired lactams with 10:1 ratio in a 50% yield. The OLA group of intermediate **2-248** has the gauche interaction with both methyl groups, and this may confer this intermediate with higher energy (Figure 77). The existence of two methyl groups do not bring large hindrance to intermediate

2-246. Hence, 10:1 selectivity may be produced due to the energy difference between **2-246** and **2-248**.

Table 21. Condition-screening for allylic azides **2-126**.

2-126a **2-127a** **2-127b**

Entry	Condition	Ratio	Yield
		(2-127a : 2-127b)	(2-127a + 2-127b)
		SM and CHO	
1	1.5 eq SnCl ₄ , DCM, reflux	(20%)	nd
2	3 eq SnCl ₄ , DCE, reflux	messy	nd
3	3 eq TiCl ₄ , DCM, reflux	2:1: 0.4 (sm)	nd
4	1.5 eq TiCl ₄ , DCE, reflux	10:1	50%

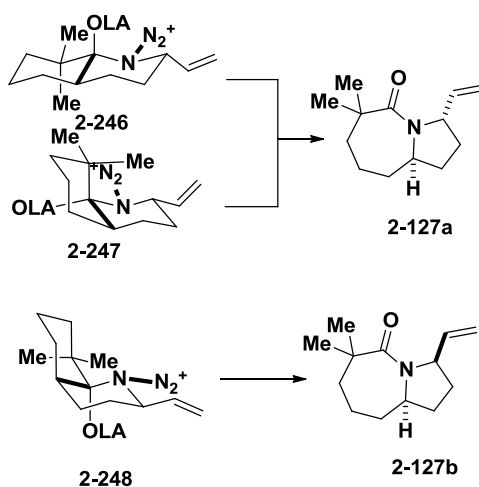
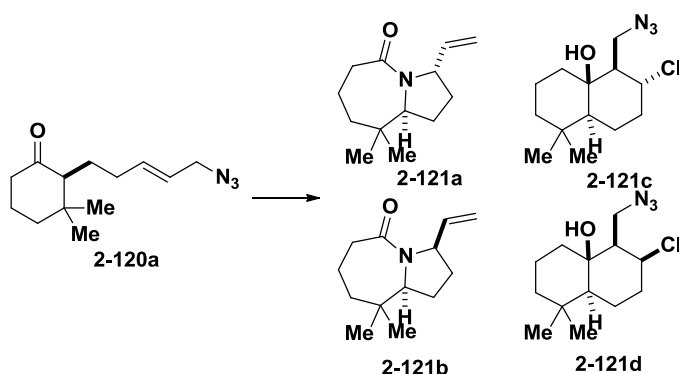


Figure 77. Proposed intermediates to **2-127a** and **2-127b**.

For allylic azides **2-120** containing 3,3-dimethyl substituted cyclohexanone, a very interesting result was obtained (Table 22). When the temperature treating allylic azides **2-120** with TiCl_4 was changed from 0 °C to refluxing in DCE, the ratio of lactams **2-121a** and **2-121b** changed from 1:1.1 to 1.4:1. However, the ratio changed from 4:1 to 35:1 when carrying out this experiment with SnCl_4 .

Table 22. Condition-screening for allylic azides **2-120**.



Entry	Condition	Ratio		
		[2-121a : 2-121b (: 2-121c : 2-121d)]	Yield (2-121a + 2-121b)	Yield (2-121c + 2-121d)
1	1.5 eq TiCl_4 , DCM, 0 °C	1.0:1.1:0.4:0.1	25%	8%
2	1.5 eq TiCl_4 , DCM, reflux	1:1.1	61%	
3	1.5 eq TiCl_4 , DCE, reflux	1.4:1	77%	
4	1.5 eq SnCl_4 , DCM, 0 °C	4:1	14%	
			22%(brsm)	
5	1.5 eq SnCl_4 , DCM, reflux	30:1	57%	
6	1.5 eq SnCl_4 , DCE, reflux	35:1	55%	

Due to the relatively weaker Lewis acidity of tin chloride, O-Sn bond is 2.30 Å; but O-Ti bond is 2.14 Å.¹⁰² This bond length difference may contribute to the difference of selectivity. The syn-axial interaction between axial methyl group and axial O-SnCl₃ group in the intermediate **2-249-Sn** may be relatively smaller in comparison with the *syn*-pentane interaction between axial methyl group and alkyl side-chain in the intermediate **2-251-Sn** (Figure 78). This could be the reason why SnCl₄ can afford high diastereoselectivity. However, this might be not true for TiCl₄ due to short O-Ti bond, and the syn-axial interaction in **2-249-Ti** may be matchable with the *syn*-pentane interaction in **2-251-Ti**.

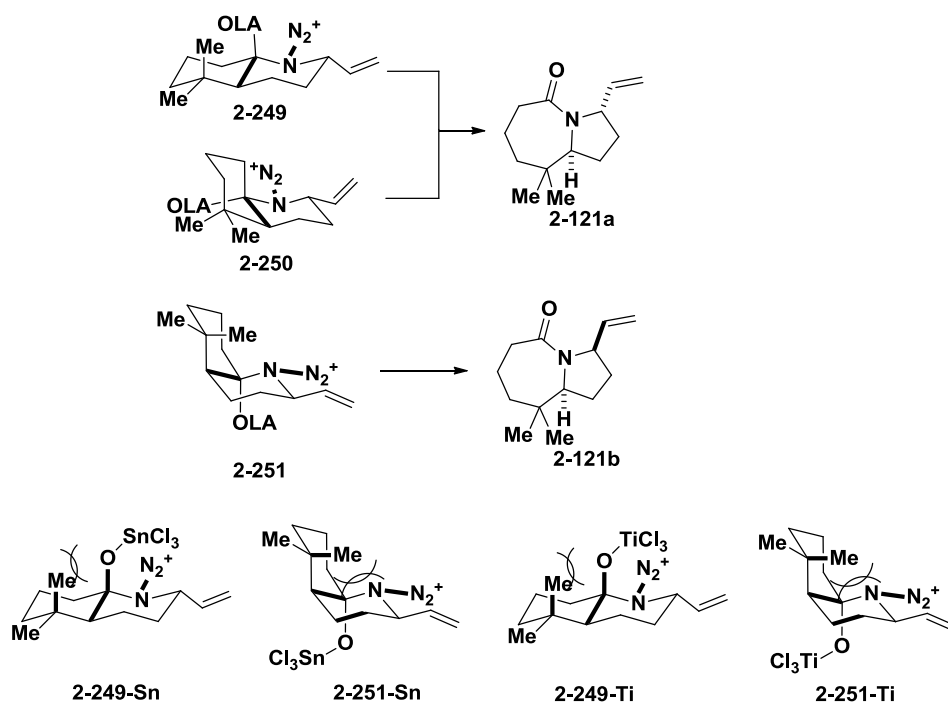
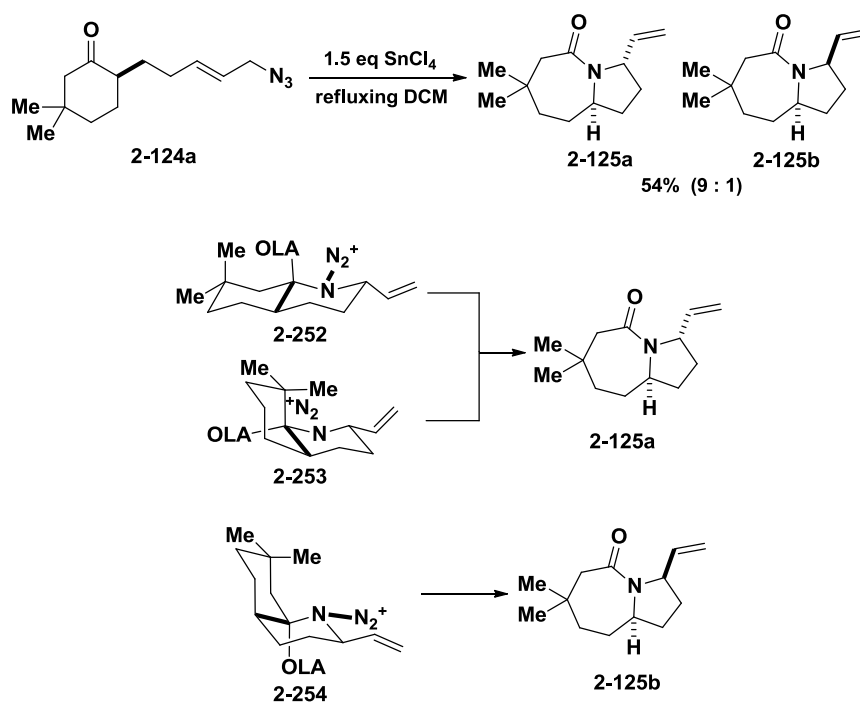


Figure 78. Proposed intermediates to **2-121a** and **2-122b**.

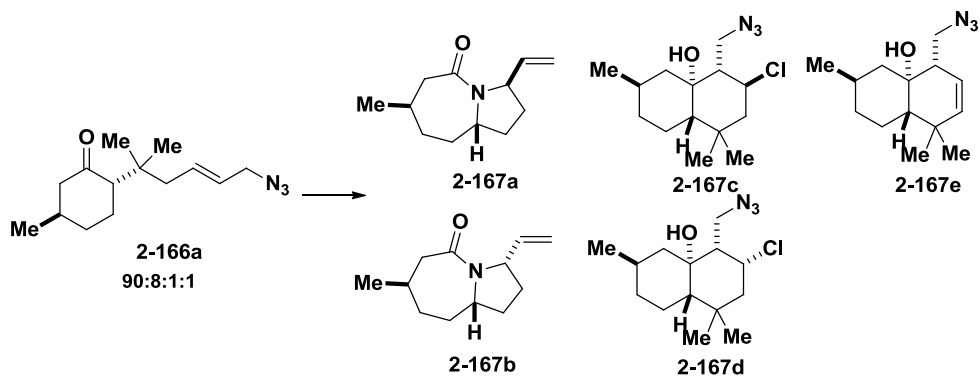
When allylic azides **2-124** were treated with SnCl₄, lactams **2-125a** and **2-125b** were obtained in a 54% yield with 9:1 diastereoselectivity (Scheme 63). This reaction under the promotion of TiCl₄ under different temperatures should also be investigated.



Scheme 63. Generation of lactams **2-125a** and **2-125b**.

Although the population of internal isomers **2-166c** and **2-166d** is much lower (~2%; not shown), lactams **2-167a** and **2-167b** were obtained in the modest yield with the ratio ranged from 1:1.7 to 1.6:1 (Table 23). The success of this reaction demonstrated the power of this combination. Like the conversion from azides **2-120** to lactams **2-121**, TiCl_4 and SnCl_4 provided the different selectivity pattern. Titanium favored the generation of lactam **2-167b**; however, tin favored the production of **2-167a**. Right now, it remains unclear why different metal plays so important of a role in the energy difference between **2-255** and **2-257** (Figure 79).

Table 23. Condition-screening for allylic azides **2-166**.



	Condition	Yield	Ratio (2-167a : 2-167b : 2-167c : 2-167d)
1	1.5 eq TiCl ₄ , DCM, rt	64% (2-167c + 2-167d)	0:0:15:1
2	1.5 eq TiCl ₄ , DCM, reflux	10% (2-167a + 2-167b) 57% (2-167c + 2-167d)	1:1.2:11:1
3	1.5 eq TiCl ₄ , DCE, reflux	33% (2-167a + 2-167b) 33% (2-167c + 2-167d + 2-167e)	1:1.7:2.2:0.1:0.2 (167e)
4	1.5 eq SnCl ₄ , DCM, reflux	63% (2-167a + 2-167b)	1.3:1:0:0
5	1.5 eq SnCl ₄ , DCE, reflux	50% (2-167a + 2-167b)	1.6:1:0:0

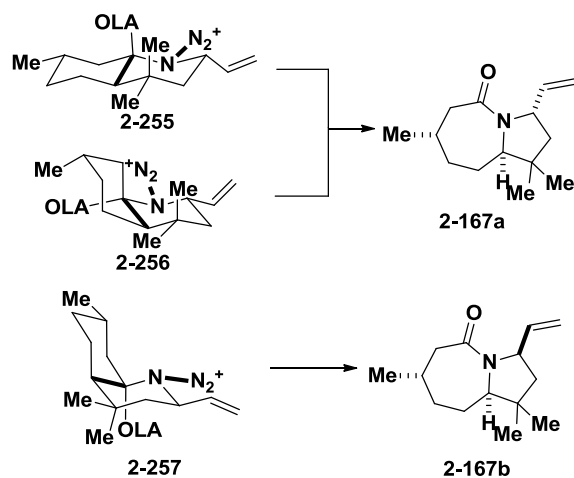
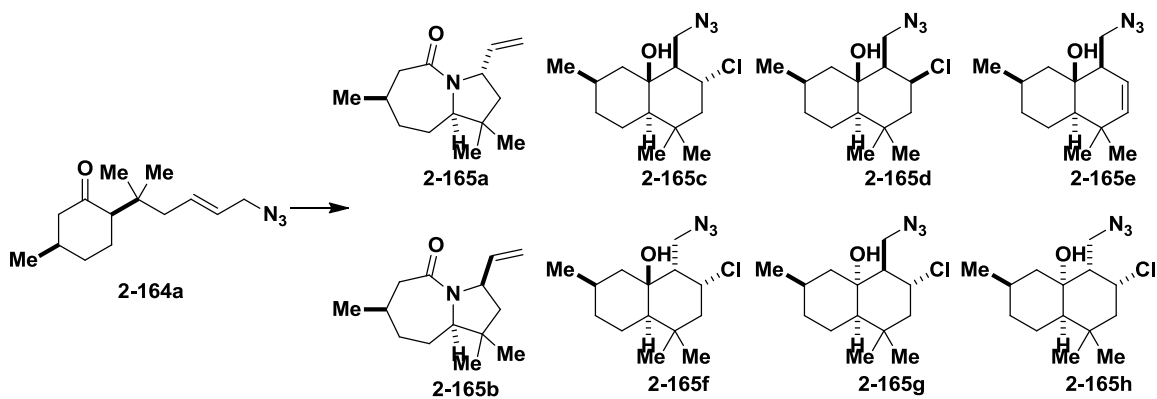


Figure 79. Proposed intermediates to **2-167a** and **2-167b**.

TiCl₄ and SnCl₄ also provided the different selectivity pattern for the conversion of azides **2-164** to lactams **2-165a** and **2-165b** (Table 24 and Figure 80). The ratio for titanium ranged from 1:4 to 1:2.5; however, it was from 4:1 to 7:1 for tin.

Table 24. Condition-screening for allylic azides **2-164**.



		Ratio
Condition	Yield	(2-165a : 2-165b : 2-165c :
		2-165d : 2-165e : 2-165f :
		2-165g : 2-165h)
1	30% (2-165a + 2-165b)	0.24:1
	21% (2-165c + 2-165d + 2-165e)	
	3% (2-165f)	
	2% (2-165g + 2-165h)	
2	1.5 eq TiCl ₄ , DCE, reflux	1:2.5
3	1.5 eq SnCl ₄ , DCM, reflux	4:1
4	1.5 eq SnCl ₄ , DCE, reflux	7:1

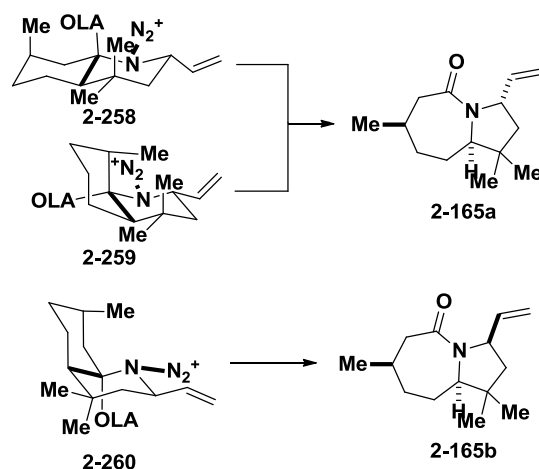


Figure 80. Proposed intermediates to **2-165a** and **2-165b**.

After the studies of substituents around the six-membered ring, we focused our attentions on the α -substituent of the ketone (Figure 81). Through the above cases, we have learned that low selectivity was obtained due to the possible attacks of azide, of the equatorial side chain, on both faces of ketone. If the side chain is forced to the axial position, only one face of ketone is accessible, and then high selectivity can be obtained. We tried to put the substituents on the α -position of ketone and then to force the side chain to the axial position.

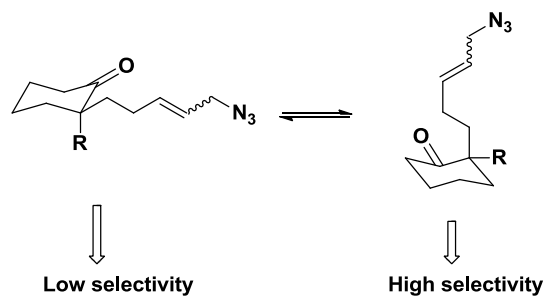


Figure 81. Selectivity pattern of two conformers.

Because methyl group and alkyl side chain have a similar A value, a comparative percentage of equatorial and axial conformers are expected. Then, the more contribution from **2-262** is expected due to the more population of axial conformer **ax-2-134c**, and hence high

ratio of **2-135a** and **2-135b** was expected (Figure 82). Methyl-substituted azides **2-134** were treated with TiCl_4 or SnCl_4 to afford lactams **2-135a** and **2-135b** in a modest yield with 1.1:1 ratio (Table 25). That indicated that the flipping of axial and equatorial conformers, which may have the lower energy barrier, is much faster than the combination, as the allylic azide rearrangement is.

Table 25. Condition-screening for allylic azides **2-134**.

2-134a 2-135a 2-135b

Entry	Condition	Ratio	Yield
		(2-135a: 2-135b)	(2-135a+2-135b)
1	1.5 eq SnCl_4 , DCM, reflux	1.1:1	57%
2	1.5 eq TiCl_4 , DCE, reflux	1.1:1	75%

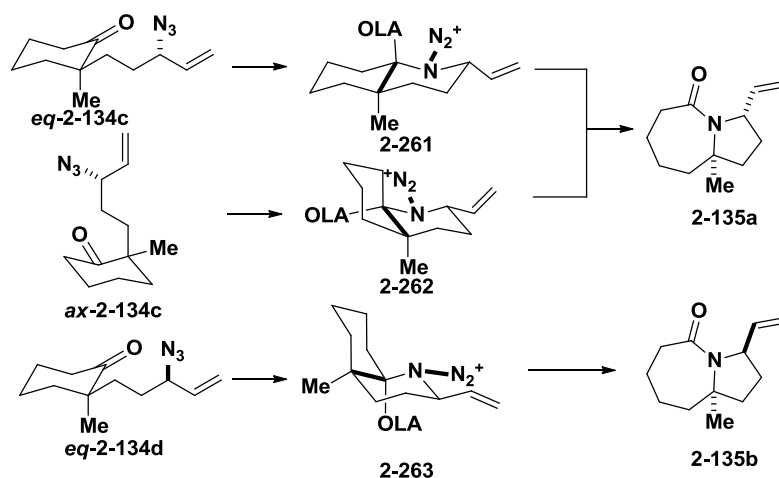
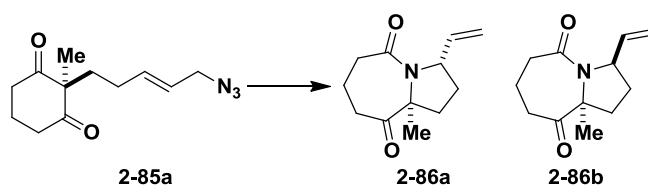


Figure 82. Proposed intermediates to **2-135a** and **2-135b**.

If an additional carbonyl group is added to 3-position of cyclohexanone, the azide can have two attacking options; and the probability of this reaction going through the most stable conformation is greatly increased. Several conditions were screened for azides **2-85**, and lactams **2-86a** and **2-86b** were obtained in a 1:5 ratio (Table 26). This indicated that intermediate **2-266** is most stable (Figure 83).

Table 26. Condition-screening for allylic azides **2-85**.



	Condition	Yield	Ratio (2-86a : 2-86b)
1	3 eq SnCl ₄ , DCM, reflux	26%	1:5
2	2.1 eq TiCl ₄ , DIEA, DCM, rt		No reaction
3	2.1 eq TiCl ₄ , pyridine, DCM, rt		No reaction
4	1.5 eq SnCl ₄ , DCM, reflux (after 15 h, no solvent)	43%	1:5
5	1.5 eq SnCl ₄ , DCM, reflux, 3 days	17% (20% brsm)	1:3

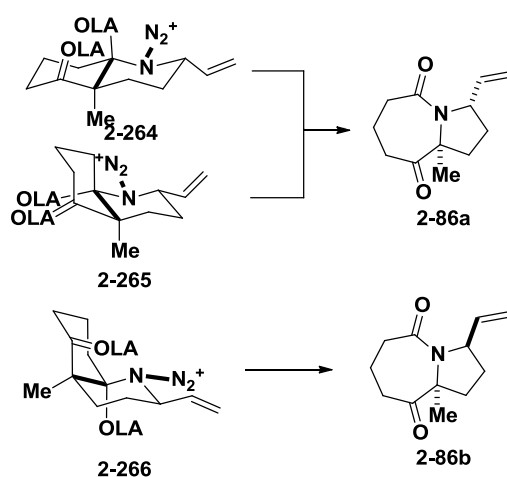
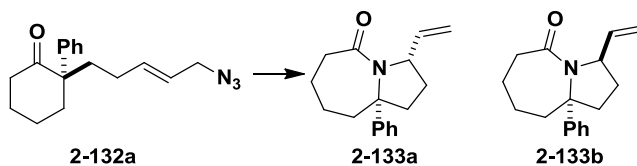


Figure 83. Proposed intermediates to **2-86a** and **2-86b**.

The bigger the group at the α -position of ketone, the higher population of axial conformers. This also increased the flipping energy barrier of chair conformation in the cyclohexane system. When phenyl-substituted ketone **2-132** was treated with TiCl_4 , lactams **2-133a** and **2-133b** were obtained in a 75% yield with 5:1 ratio (Table 27 and Figure 85).

Table 27. Condition-screening for allylic azides **2-132**.



Entry	Condition	Ratio	Yield
		(2-133a : 2-133b)	(2-133a + 2-133b)
1	1.5 eq SnCl_4 , DCM, reflux		No reaction
2	1.5 eq TiCl_4 , DCE, reflux	5:1	75%

The equilibration between two conformers of **2-270** provided the deeper understanding of this combination (Figure 84). For 1-phenyl 1-methylcyclohexane, it is not

like what we expected **eq-2-270** to be the predominant conform, based on the A value difference (A value of phenyl is 3.0 kcal/mol; A value of Me is 1.70 kcal/mol). Actually, **ax-2-270** is 0.34 kcal/mol more stable than **eq-2-270**.¹⁰³ For **eq-2-270**, the rotation of phenyl ring cause different steric hindrance. When phenyl ring is in the bisector of cyclohexane, two hydrogens of methyl group and equatorial phenyl group have great repulsive force. If phenyl ring is perpendicular to the bisector of cyclohexane, there are still some interactions between methylene hydrogens and hydrogens in the phenyl ring. Hence, **ax-2-270** is of lowest energy. But there is one carbonyl group for **2-271** in one side of 1,1-disubstituted cyclohexane system. We tried to detect the energy difference between **eq-2-271** and **ax-2-271** using NMR technique. Even although the sample was cooled to -100 °C, no difference in the ¹³C NMR was detected.

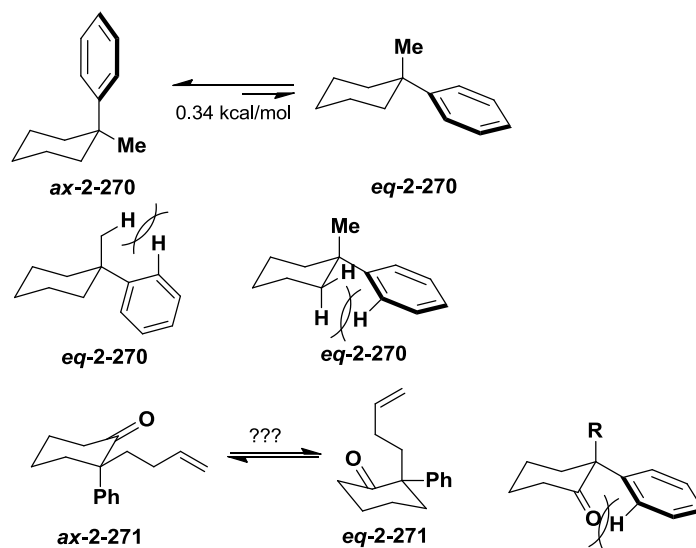


Figure 84. Conformational analysis of phenyl-substituted cyclohexanes.

Because phenyl group is preferred to be at the axial position of cyclohexane, intermediate **2-267** may be slightly favored due to the phenyl group in the axial positions of

both 6-membered ring systems (Figure 85). This is the reason why only 5:1 ratio was obtained for this substrate.

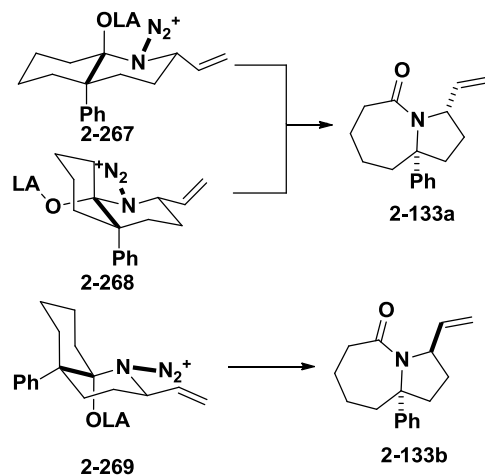
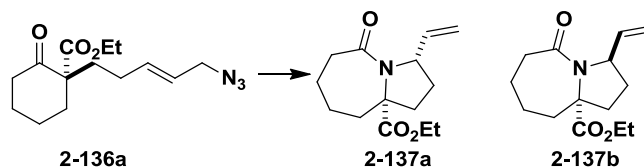


Figure 85. Proposed intermediates to **2-133a** and **2-133b**.

α -Keto ester **2-136** was tested for this combination, and only 1.7:1 ratio was obtained (Table 28). Because there are two carbonyl groups in this molecule, it is suspected that metal can coordinate two carbonyl groups to form an intramolecular bond (**2-273** and **2-274**), and then this make the intermediate with lower energy than the molecule with two metals coordinating two carbonyl groups (Figure 86). This may be the reason why poor selectivity was obtained.

Table 28. Condition-screening for allylic azides **2-136**.



Entry	Condition	Ratio	Yield
		(2-137a : 2-137b)	(2-137a + 2-137b)
1	3 eq TiCl ₄ , DCE, reflux	1.7:1	55%
2	1.5 eq TiCl ₄ , DCE, reflux	1.6:1	45%

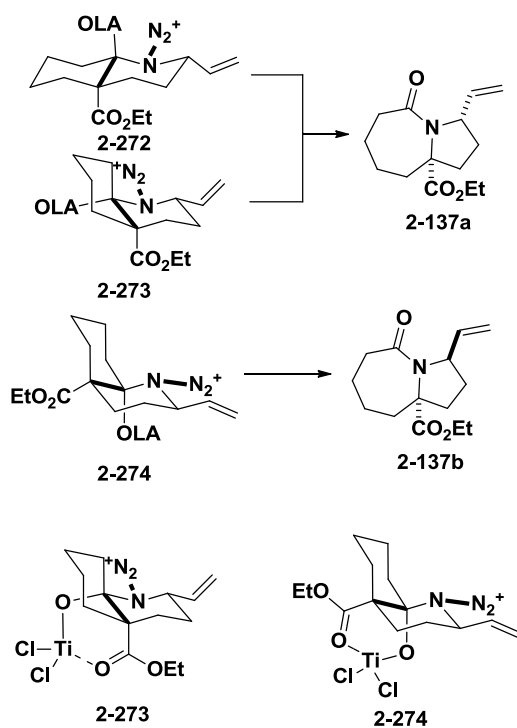
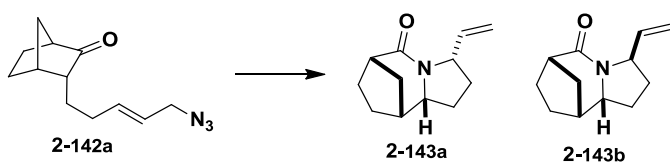


Figure 86. Proposed intermediates to **2-137a** and **2-137b**.

Allylic azides **2-142** were expected to afford lactams **2-143a** and **2-143b** with high selectivity due to the facial attack only from one face (Table 29). 15:1 ratio was obtained

when treating allylic azides **2-142** with TiCl_4 in refluxing dichloroethane. Azide in the endo-side chain can not reach the carbonyl group from exo face (Figure 87). Vinyl group is in the pseudo-equatorial position of boat conformation **2-275**; however, it is at the pseudo-axial position for **2-276**. Hence, lactam **2-143a** was the major product.

Table 29. Condition-screening for allylic azides **2-142**.

			
	Condition	Yield	Ratio
1	1.5 eq SnCl_4 , DCM, reflux	No reaction (15% CHO)	
2	1.5 eq SnCl_4 , DCE, reflux	Messy; no product	
3	1.5 eq TiCl_4 , DCM, reflux	48%	9:1
4	1.5 eq TiCl_4 , DCE, reflux	65%	15:1

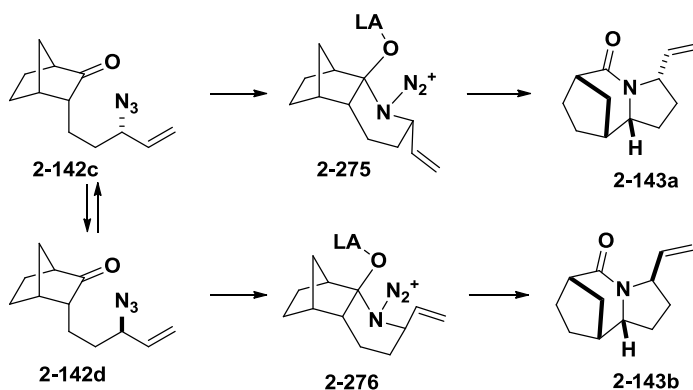


Figure 87. Proposed intermediates to **2-143a** and **2-143b**.

Allylic azides **2-140**, like **2-142**, provided high selectivity (>20:1) of lactams **2-141a** and **2-141b** for the combination (Table 30). The similar mechanistic analysis was also applied here (Figure 88).

Table 30. Condition-screening for allylic azides **2-140**.

<div><p>2-140a</p><p>2-141a</p><p>2-141b</p><p>2-141c</p><p>2-141d</p><p>2-141e</p><p>2-141f</p></div>			
	Condition	Yield	Ratio
1	1.5 eq SnCl ₄ , DCM, reflux		No reaction (20% CHO)
2	1.5 eq SnCl ₄ , DCE, reflux		Messy; no product
3	1.5 eq TiCl ₄ , DCM, reflux	60%(schmidt) 8% (prins)	5.6:0.24:0.86:1:0.05:0.4
4	1.5 eq TiCl ₄ , DCE, reflux	70%(schmidt) 4% (prins)	14.2:0.16:0.84:0.47:0.05:0.1

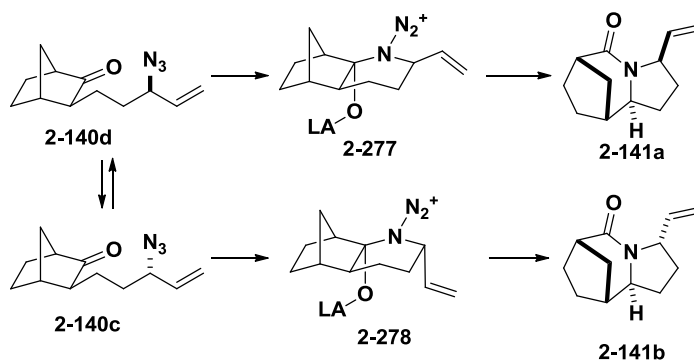
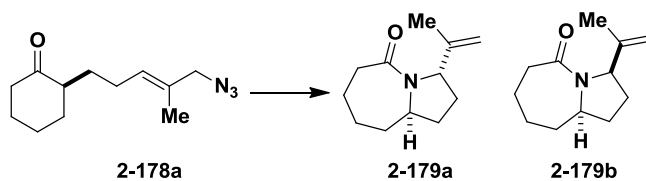


Figure 88. Proposed intermediates to **2-141a** and **2-141b**.

Another strategy to increase selectivity would be to increase the bulkiness of the vinyl group. Then allylic azides **2-178** were prepared and tested for this combination; and a 5:1 ratio was obtained (Table 31 and Figure 89).

Table 31. Condition-screening for allylic azides **2-178**.



	Condition	Yield	Ratio (2-179a : 2-179b)
1	1.5 eq SnCl ₄ , DCM, rt		messy
2	1.5 eq SnCl ₄ , DCM, reflux	19%	7:1
3	1.5 eq SnCl ₄ , DCM, reflux	26%	5:1
4	1.5 eq SnCl ₄ , DCM, reflux	24%	5:1
5	1.5 eq SnCl ₄ , DCE, reflux		messy

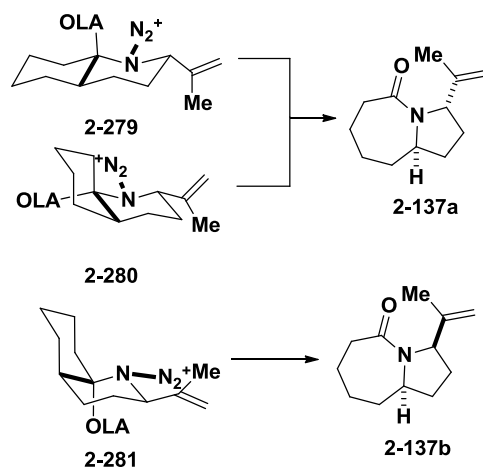
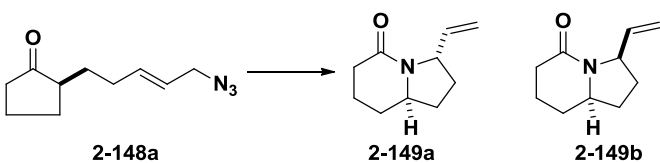


Figure 89. Proposed intermediates to **2-179a** and **2-179b**.

In addition to the six-membered cyclohexanones, cyclopentanone allylic azides **2-148** were also tested for this combination (Table 32). However, only a 1.7:1 ratio of lactams **2-149a** and **2-149b** was obtained. The energy difference between **2-282**, **2-283** and **2-284** remains unclear at this stage (Figure 90).

Table 32. Condition-screening for allylic azides **2-148**.

			
	Condition	Ratio	Yield
1	3 eq SnCl ₄ , DCM, r.t.	5:3	39%
2	1.5 eq SnCl ₄ , DCM, reflux	5:3	28%
3	3 eq SnCl ₄ , DCM, reflux	5:3	29%
4	3 eq TiCl ₄ , DCM, r.t.	5:4	30%

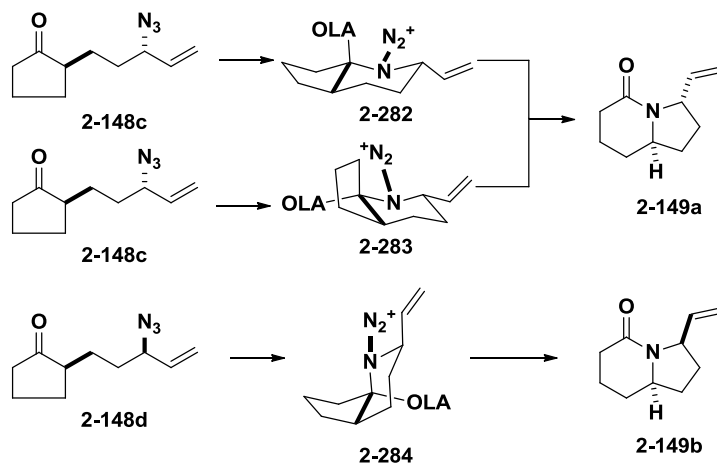
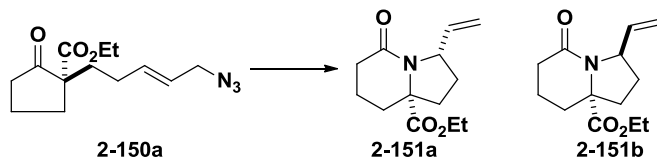


Figure 90. Proposed intermediates to **2-149a** and **2-149b**.

This combination was also carried out on the ethyl ester substituted allylic azides **2-150**, and a reversed 1:3.5 ratio was obtained. As mentioned in Figure 86, there may be mutual chelation between two carbonyl groups. This could stabilize intermediate **2-287**, thus producing lactam **2-151b** as the major product (Table 33 and Figure 91).

Table 33. Condition-screening for allylic azides **2-150**.



	Condition	Result	Ratio
1	3 eq TiCl ₄ , DCM, -78 °C	mixture	
2	3 eq TiCl ₄ , DCM, 0 °C		1:2
3	3 eq TiCl ₄ , toluene, 100 °C		1:5

4	3 eq TiCl ₄ ·2THF, DCM, rt,	Conv. 50%	1:3
5	3 eq TiCl ₄ ·2THF, DCM, reflux,	Conv. 60%	1:2
6	3 eq TiCl ₄ ·2THF, toluene, reflux,		1:2
7	3 eq TiCl ₄ ·2THF, DCE, reflux	16%	3:5
8	TfOH, DCM, r.t.	messy	
9	TFA, DCM, r.t.	26%	1:3.5
10	3 eq SnCl ₄ , DCM, r.t.		1:4
11	3 eq BF ₃ ·OEt ₂ , DCM, r.t.		1:7
12	0.9 eq TiCl ₄ , DCM, 0 °C		4:5

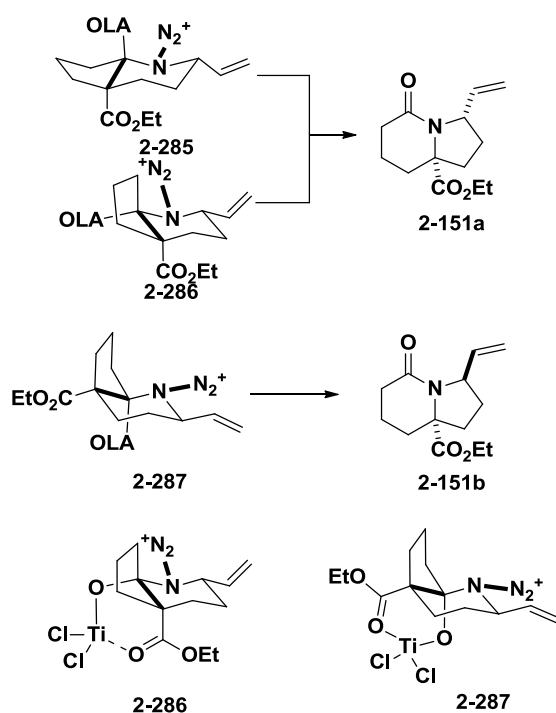


Figure 91. Proposed intermediates to **2-151a** and **2-151b**.

Allylic azides on linear ketones were also prepared and tested for this combination. Allylic azides **2-172** were prepared and tested for this combination, and a 2:1 ratio was obtained (Table 34). Depending on the orientation of carbonyl group, its attack to azide of **2-172c** produced two intermediates **2-288** and **2-289** (Figure 92). Likewise, reaction of **2-172d** produces the corresponding **2-290** and **2-291**. In **2-290** and **2-291**, there is a strong repulsive force between the syn axial methyl group and the OLA or methyl group from the methyl ketone. Right now, it remains unclear why only 2:1 ratio was obtained.

Table 34. Condition-screening for allylic azides **2-172**.

	Condition	Yield	Ratio
1	1.5 eq TiCl ₄ , DCM, reflux	33%	2:1
2	1.5 eq SnCl ₄ , toluene, reflux	messy	
3	1.5 eq SnCl ₄ , CHCl ₃ , reflux	16%	2:1
4	1.5 eq SnCl ₄ , DCE, reflux	31%	2:1

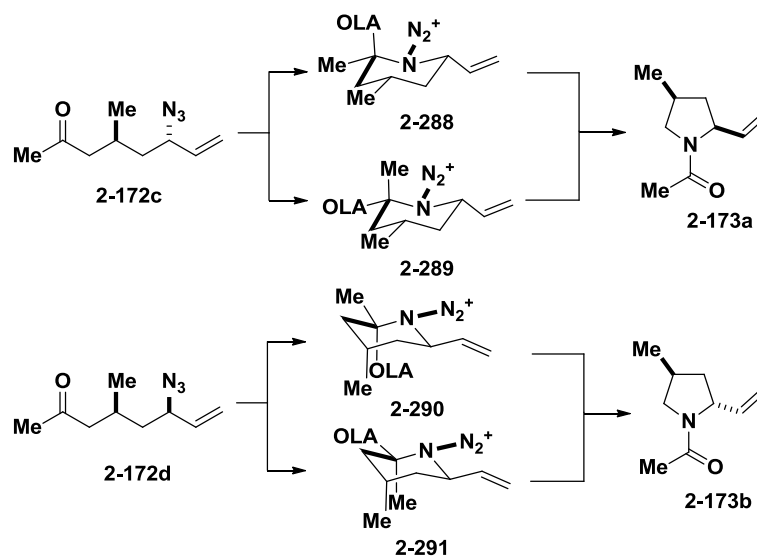
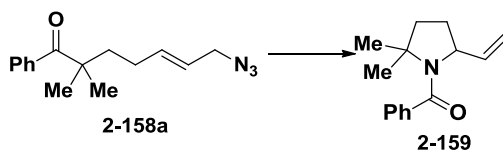


Figure 92. Proposed intermediates to **2-173a** and **2-173b**.

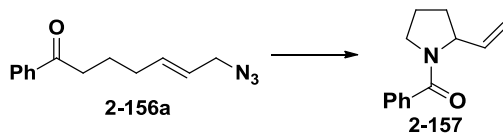
Lactams **2-159** were prepared from linear ketones **2-158** in the modest yields although the existence of bulky carbonyl groups (Table 35). However, a 25% yield of lactam **2-157** was obtained for azides **2-156** (Table 36), possibly resulting from the poor electrophilicity of the carbonyl group here.

Table 35. Condition-screening for allylic azides **2-158**.



	Condition	Yield
1	1.5 eq TiCl ₄ , DCM, r.t.	47%
2	1.5 eq SnCl ₄ , DCM, 0 °C	44%
3	1.5 eq SnCl ₄ , DCM, r.t.	51%
4	1.5 eq SnCl ₄ , DCM, reflux	54%

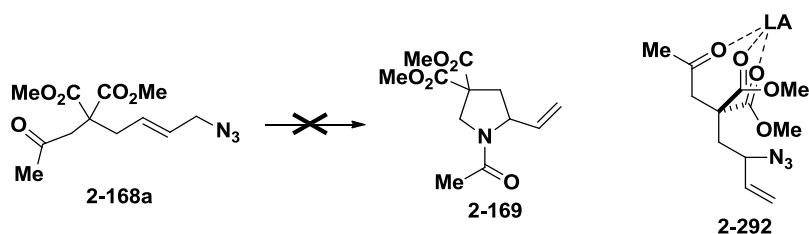
Table 36. Condition-screening for allylic azides **2-156**.



	Condition	Yield
1	3 eq TiCl ₄ , DCM, r.t.	25%
2	3 eq SnCl ₄ , DCE, reflux	messy

3	3 eq SnCl ₄ , toluene, reflux	messy
4	1.5 eq SnCl ₄ , DCM, reflux	aldehyde

Various conditions were screened for the preparation of lactam **2-169**; however, no one was successful (Scheme 64). The formation of intermediate **2-292** could block the way azide attacks the carbonyl group.



Scheme 64. Attempts to prepare lactam **2-169**.

2.7 Dihedral angle discussion

In Section 2.6, high diastereoselectivity was obtained on two impressive examples due to the facial selectivity of carbonyl groups (Figure 93). In each case, only one face of ketone is accessible for the attack by the azide. The first example is the conversion of **2-130** to **2-131a** through the chair conformation intermediate **2-240**. Because of the axial side chain, the azide can only attack the carbonyl group from its equatorial face. Hence, the syn lactam **2-131a** is the major product, resulting from the competition between equatorial and axial vinyl group. The opposite diastereoselectivity is observed in the conversion of **2-140** to **2-141** through the boat conformation intermediate **2-277**. Because of the exo side chain, the azide can only attack the carbonyl group from exo direction. Hence, the anti lactam **2-141a** is the major product. In the above two cases, one is with syn major product arising from a chair conformation intermediate; and the other is with anti major product from boat conformation

intermediate. This result forced us to consider which parameter can determine the 6-membered conformation is chair or boat in this system.

In contrast, for most cyclohexanone examples with the side chain at the equatorial position, both faces of the carbonyl group can be accessed by the azide; and the formed two intermediates (e.g. **2-206** and **2-209**), with the similar energy (less than 0.5 kcal/mol), produced both lactams with low selectivity.

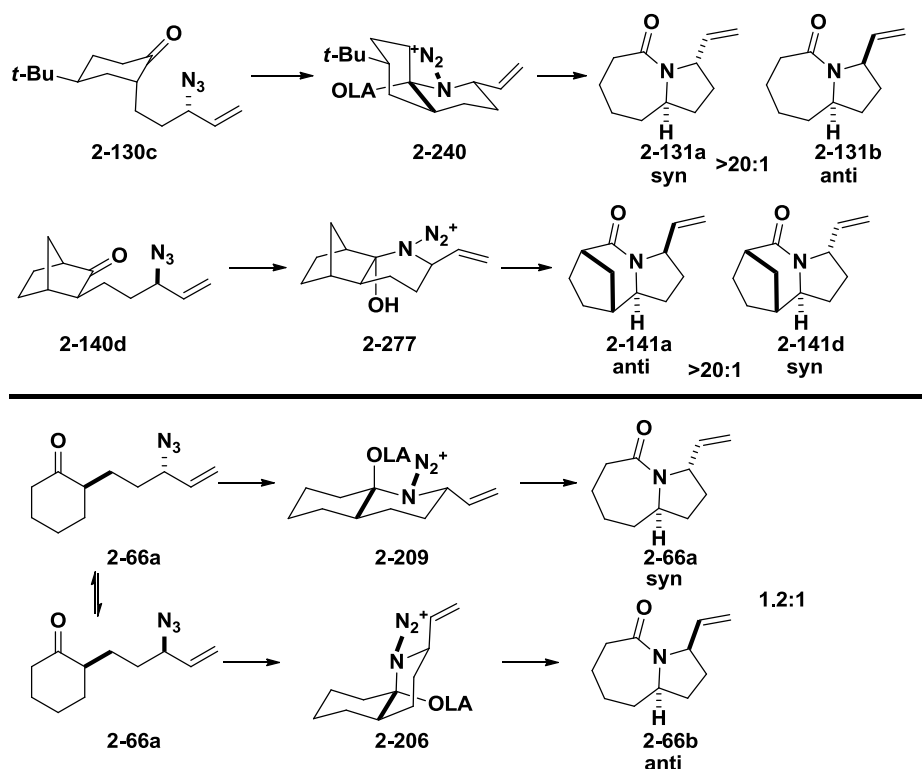


Figure 93. Selectivity comparison.

The dihedral angle between the side chain and ketone plane is considered. For the cyclohexanone system, the equatorial side chain has a dihedral angle of 9.8° with carbonyl group. If the side chain is switched to the axial position, this dihedral angle becomes 107.1° . For the norcamphor system, the dihedral angle is around 60° regardless of the exo- or endo-

orientation. But the dihedral angle for exo-side chain is slightly larger, and this may be the reason why higher selectivity is obtained for endo-azides **2-140**.

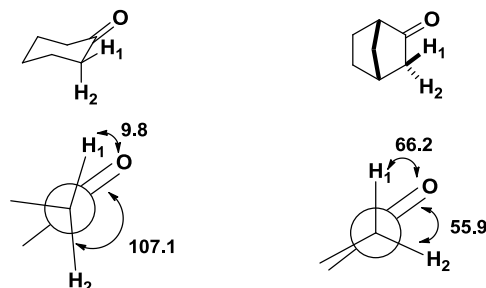


Figure 94. Dihedral angles of cyclohexanone and norcamphor systems.

If the connection between dihedral angle and selectivity is made, the relationship curve should be like what is shown in Figure 95. For the allylic azides with cyclic ketones, the formed six-membered intermediate, upon the treatment of Lewis acid, can adopt any of the possible conformations cyclohexane can have, such as chair, boat and half-chair conformations (Figure 96). When dihedral angle is at 0° , there are two stable chair-conformation intermediates with equal energies, which can produce equal amounts of both lactams. When dihedral angle is around 60° , only one face of ketone is accessible and the anti lactam is produced through boat conformation intermediate as the major product. When dihedral angle is around 90° , the intermediate with half-chair conformation may be formed, leading to the syn lactam as the major product. When dihedral angle is around 110° , only one face of ketone is accessible and the syn lactam is produced as the major product through chair conformation intermediate. If the dihedral angle is above 120° , the azide of side chain can not reach the carbonyl group to form a six-membered ring.

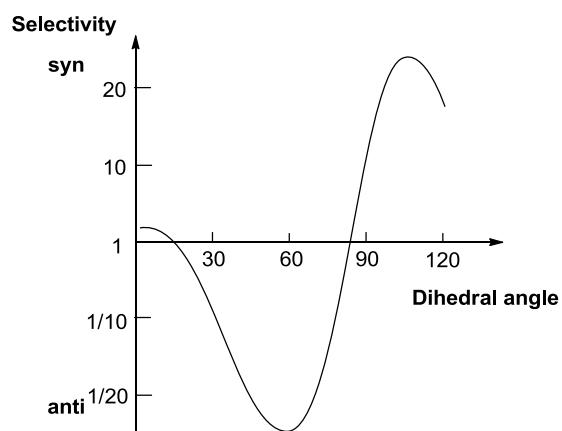


Figure 95. The relationship between selectivity and dihedral angle.

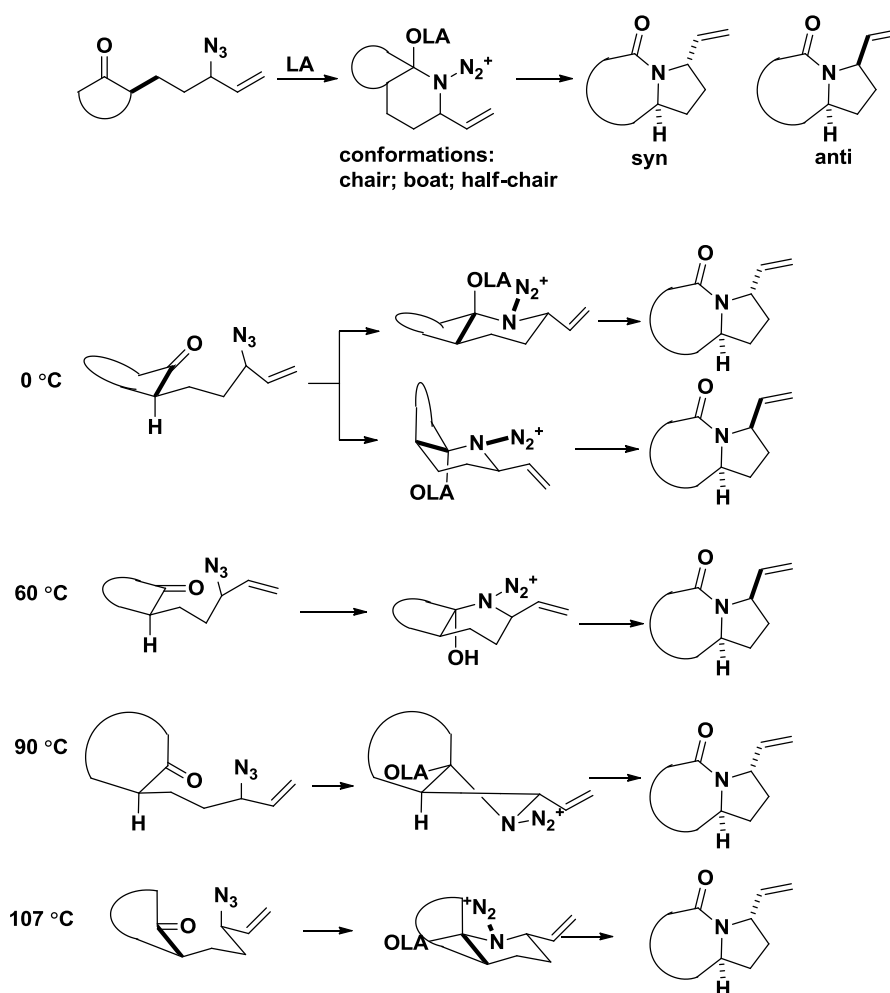


Figure 96. General scheme for the selectivity.

Definitely, the above analysis is purely theoretical, and the impact of substituents on the ketone part were not taken into consideration.

More examples should be tested to confirm this hypothesis. We re-examined the result of cyclopentanone **2-148**, which produce lactams **2-149a** and **2-149b** with 1.7:1 ratio, and found that it matched with our hypothesis. The carbonyl group of cyclopentanone, whose conformation is to be discussed in detail in chapter 3, resides on the least puckered carbon in the five-membered ring in order to produce the most stable [5,6]-fused intermediate. The dihedral angle between side chain of **2-149** and the ketone plane is less than 20° , so a 1.7:1 ratio fits our analysis. High selectivity would be expected due to the dihedral angle of cyclobutanone, bicyclo[2.2.2]octan-2-one, and tropinone.

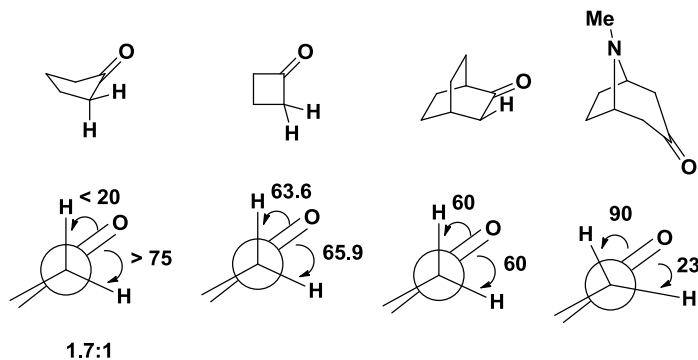


Figure 97. Novel cyclic ketones with different dihedral angles.

The utilization of chair or boat conformation to analyze the stereochemical outcomes of organic reactions is very common for fused bicyclic system, in which one cycle has the definite conformation. To the best of our knowledge, there is no general principle on why chair or boat conformation is used. Herein, the analysis of dihedral angle could provide some illustrations about this question.

2.8 Carbocation-mediated allylic azide preparation

Most examples we have tested so far have the vinyl group at the end. Because there is no substituent at the end of the double bond, the chiral center in the allylic azide can be reversed, such as the conversion of **2-107c** to **2-107d**, as discussed in Figure 48 (Figure 98). But, the chiral center of **2-112d** can not be reversed to **2-113**, based on a concerted sigmatropic rearrangement as discussed in Figure 49.

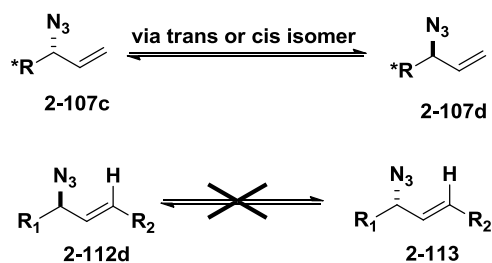
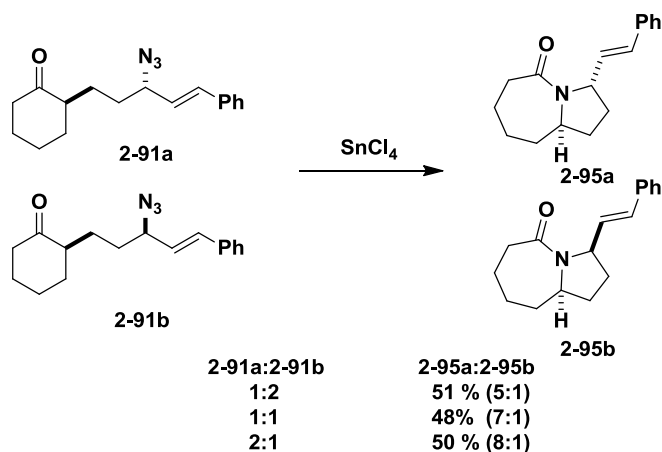


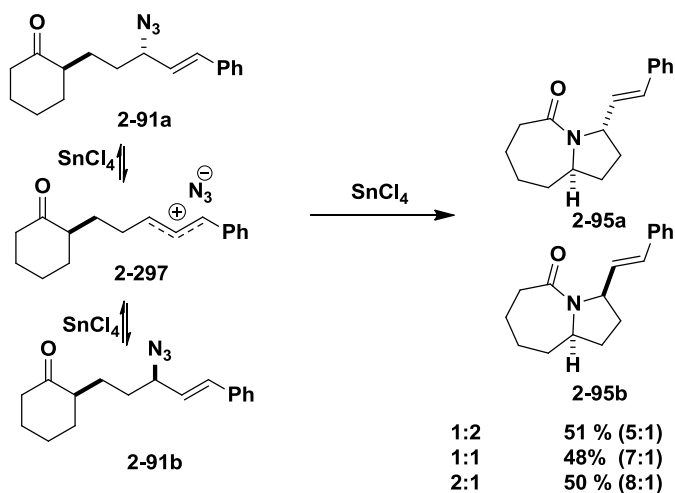
Figure 98. Reversing the chiral center in allylic azides.

Based on the sigmatropic rearrangement, if allylic azides **2-91a** and **2-91b**, whose stereochemistry is arbitrarily assigned, were treated with SnCl_4 , lactams **2-95a** and **2-95b** should be obtained with the same ratio as the ratio of **2-91a** and **2-91b**. However, when different ratios of azides **2-91a** and **2-91b** were activated, similar ratio of lactams **2-95a** and **2-95b** were obtained, with the syn lactam **2-95a** as the major product.



Scheme 65. The combination of azides **2-95a** and **2-95b**.

The result suggested that this allylic azide rearrangement is not proceeding via a fully concerted sigmatropic rearrangement. An alternative mechanism consistent with this could involve with carbocation **2-297** (Scheme 66). Ion pair collapse and re-association allows the equilibration between **2-91a** and **2-91b**, hence providing a reasonable mechanism for the selective production of lactam **2-95a**.

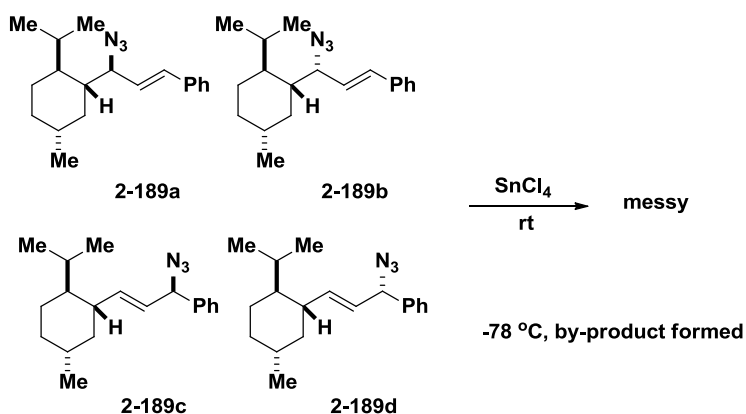


Scheme 66. Carbocation-involved allylic azide rearrangement.

In order to further examine this allylic azide rearrangement under the thermal conditions, a mixture of azides **2-91a** and **2-91b** having a 3:1 ratio was heated at 100 °C for 7

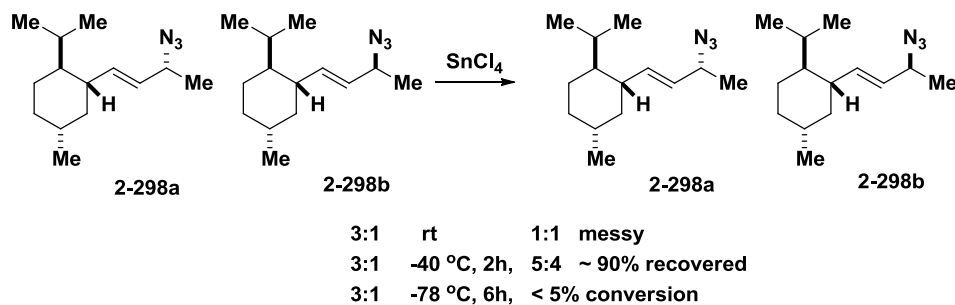
h; however, no ratio change was observed. When higher temperature was attempted, azides were decomposed in 1,2-dichlorobenzene (160 °C for 2 h) and DMSO (120 °C for 2 h). The decomposition in DMSO may result from the nucleophilicity of DMSO.

A mixture of azides **2-189a**, **2-189b**, **2-189c**, and **2-189d** was prepared, and treated with SnCl_4 to confirm whether carbocation-mediated allylic azide rearrangement exists or not (Scheme 67). However, this study did not give any positive results even though the reaction was run at -78 °C. From the spectrum of crude product, it seemed that the reorganization of allylic azide, which is to be discussed in Chapter 5, may have occurred here due to the presence of phenyl group.



Scheme 67. Testing carbocation-mediated allylic azide rearrangement.

To rule this out, when the methyl substituted allylic azides **2-298a** and **2-298b** were treated with SnCl_4 at -40 °C for 2 h, the ratio changed from 3:1 to 5:4 with a 90% recovery yield (Scheme 68). This indicated that carbocation-mediated allylic azide rearrangement actually occurred in this aliphatic case.

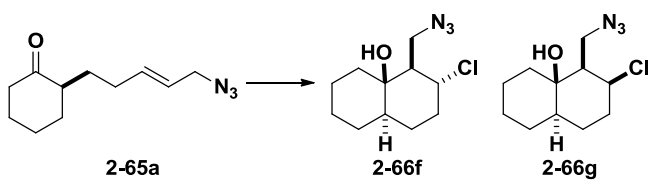


Scheme 68. Testing carbocation-mediated allylic azide rearrangement.

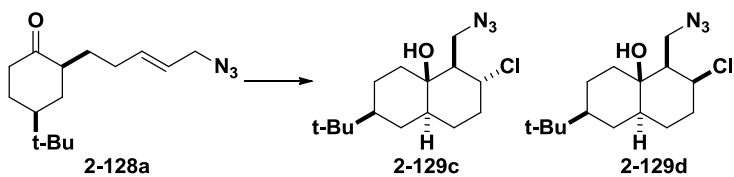
2.9 Prins reaction

In Section 2.5, a chloro-Prins reaction was mentioned as a competing side-reaction in the conditions screened for the combination of allylic azide rearrangement and the intramolecular Schmidt reaction. Most Prins side products were obtained in low yield when allylic azides were treated with TiCl_4 at various temperatures (Scheme 69). If the temperature was too high, the Schmidt reaction dominated the combination. If the temperature was too low, no reaction occurred, including a Schmidt reaction.

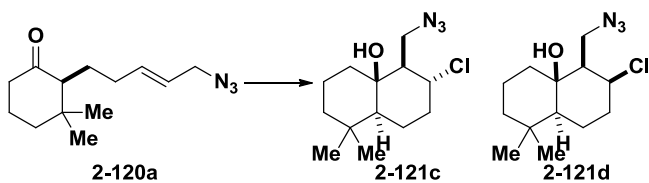
As explained in Figure 74, the anti Prins adduct is the major isomer with modest selectivity over syn isomer. Most ratios are ranged from 2.5:1 to 4:1. Only two examples were obtained in high ratio, **2-166** and **2-140**. If the temperature was increased, the chlorine-eliminated product was observed, for example **2-167e** and **2-141f**.



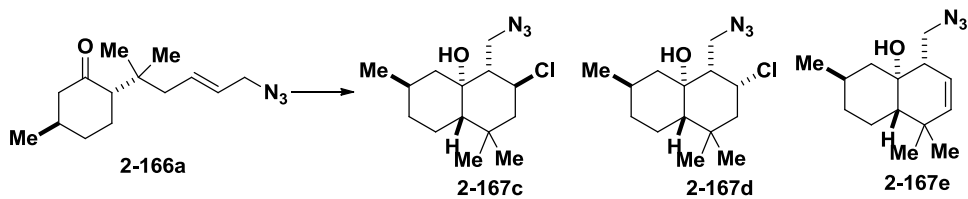
1. 1.5 eq TiCl_4 , DCM, rt 16% (1.3:0.5)



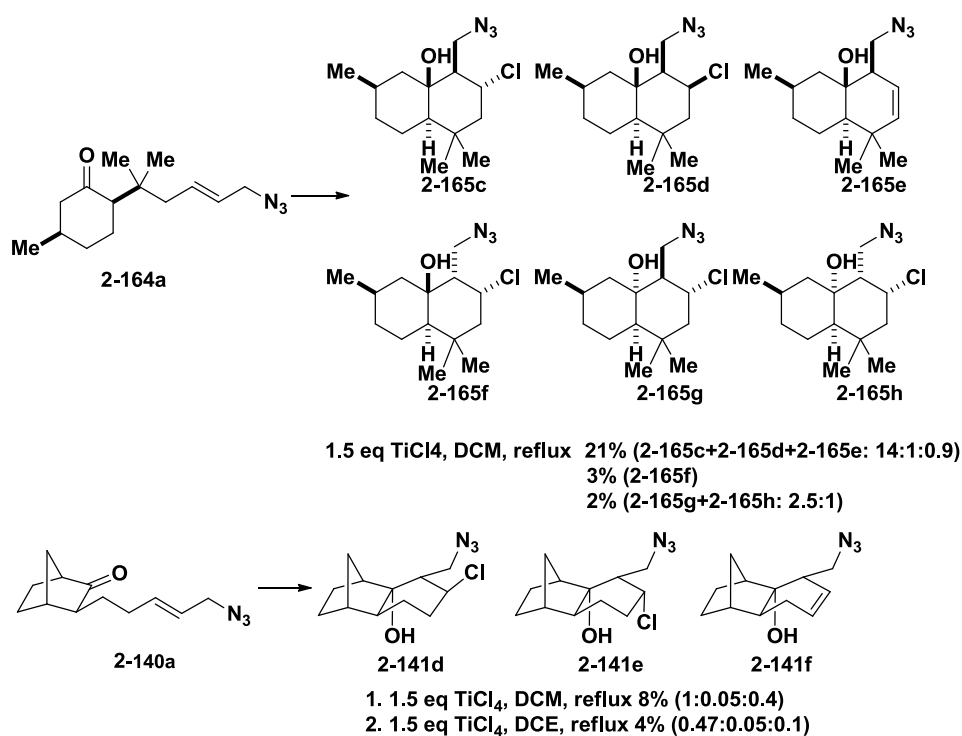
1. 1.5 eq TiCl_4 , DCM, rt 24% (1.0:0.35)
2. 1.5 eq TiCl_4 , DCM, rt; M.S. 34% (1.0:0.4)



1. 1.5 eq TiCl_4 , DCM, 0 °C 8% (4:1)



1. 1.5 eq TiCl_4 , DCM, rt 64%(15:1:0)
2. 1.5 eq TiCl_4 , DCM, reflux 57% (11:1:0)
3. 1.5 eq TiCl_4 , DCE, reflux 33% (22:1:2)



Scheme 69. The summary of halo-Prins reaction.

For the Prins reaction of azide **2-164**, there are three other Prins adducts, **2-165f**, **2-165g** and **2-165h**, besides normal Prins adducts **2-165c** and **2-165d**. They are speculated to come from an equatorial attack of equatorial azide *eq*-**2-164b** and the eq attack from axial azides *ax*-**2-164a** and *ax*-**2-164b**, respectively (Figure 99).

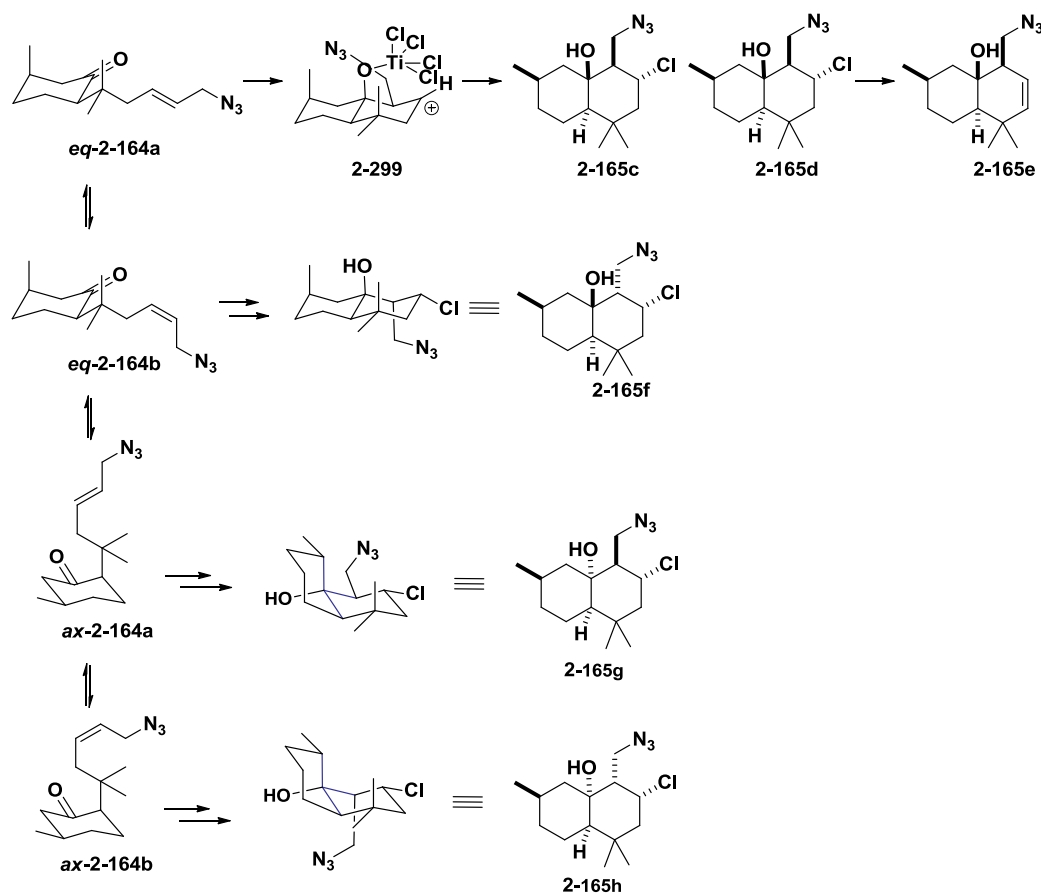


Figure 99. Proposed mechanism for Prins adduct of azide **2-164**.

2.10 Twisted amide

After understanding the stereocontrol in the combination of allylic azide rearrangement and intramolecular Schmidt reaction, we focused on the stereocontrol in the generation of twisted amides.

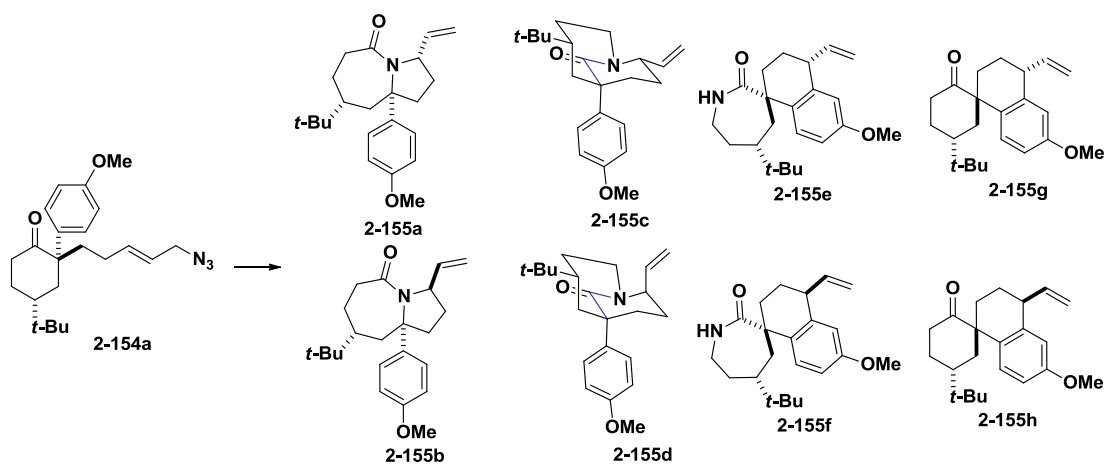
A variety of products were obtained when treating allylic azides **2-154** with various conditions (Table 37). Traditional fused amides **2-155a** and **2-155b**, the former being confirmed by X-ray (Figure 100), were obtained in most conditions, where the ratio ranged from 5:1 to 50:1 and the yield ranged from 6% to 47%. In principle, two twisted amides **2-**

155c and **2-155d** should be generated in this reaction. However, only one isomer **2-155c** was observed, in 5%–18% yield, whose structure was confirmed by X-ray (Figure 101). Twisted amide **2-155c** has similar physical and spectral data to amides **2-16** and **2-17** (Table 38).

Besides traditional and twisted amides, amides **2-155e** and **2-155d** were also obtained when more than 1 equiv of Lewis acid was used in the Schmidt reaction. Due to the quality of crystal, only partial data was collected, but it was enough to confirm the structure of amide **2-155e** (Figure 102). Excess Lewis acid can associate to the basic nitrogen of twisted amide, thus generating an allylic carbocation species (Figure 103). This subsequently reacted with electron-rich methoxy substituted aromatic ring (Friedel-Crafts reaction) to form bicyclic amides **2-155e** and **2-155f**. This further explained why no significant diastereoselectivity was observed.

Allylic azides **2-154** were treated with tin tetrachloride to afford ketones **2-155g** and **2-155h** in 31% yield, in addition to traditional amides (entry 6 in Table 37). We hypothesized that tin chloride may be not a strong enough acid to promote the Schmidt reaction in the full conversion to amide **2-155a** and **2-155b** and retard the Friedel-Crafts reaction of allylic azides **2-154** to **2-155g** and **2-155h** at the same time. Allylic carbocation **2-303**, generated from allylic azides **2-154**, directly reacted with electron-rich methoxy substituted aromatic ring to generate the corresponding ketones **2-155g** and **2-155h** (Figure 103).

Table 37. The generation of twisted amide.



	Condition	Yield	Ratio (crude)
1	1.5 eq TiCl ₄ , DCM, rt	23% (2-155a + 2-155b) 18% (2-155e + 2-155f)	1:0.2:0.9:0.9 (a:b:e:f)
2	1.5 eq TiCl ₄ , DCE, reflux	47% (2-155a + 2-155b) 39% (2-155e + 2-155f)	1:0.02:0.25:0.25 (a:b:e:f)
3	1.05 eq TiCl ₄ , DCE, reflux	40%(2-155a + 2-155c) 18%(2-155c) 9%(2-155e + 2-155f)	1:0.04:0.5:0:0.1:0.1 (a:b:c:d:e:f)
4	1.5 eq MeAlCl ₂ , DCM, rt	8% (2-155a + 2-155b) 5% (2-155c)	1:0.1:1.0:0:2.2 (a:b:c:d:sm)
5	1.5 eq MeAlCl ₂ , DCE, reflux	6% (2-155a) 14% (2-155c)	1:0:1.3:0(a:b:c:d)
6	1.5 eq SnCl ₄ , DCE, reflux	20% (2-155a + 2-155b) 31% (2-155g + 2-155h)	1:0.03:2:1 (a:b:g:h))

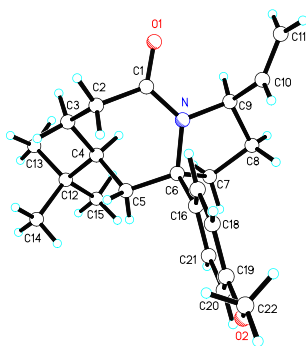


Figure 100. ORTEP representation of amide **2-155a**.

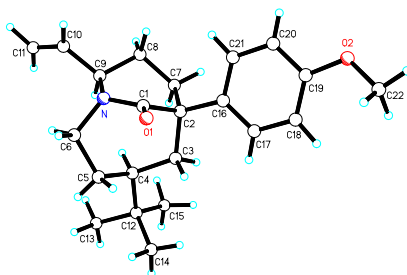


Figure 101. ORTEP representation of amide **2-155c**.

Table 38. Physical and spectral parameters of **2-155c**.

Substrate	$\tau/^{\circ}$	$\chi_N/^{\circ}$	$\chi_C/^{\circ}$	N-C(O) /Å	C=O /Å	$\nu_{C=O}$ /cm ⁻¹	¹³ C _(C=O) /ppm
Kirby (2-13)	90.5	60.0	0.0	1.475	1.196	1732	200
Aubé (2-16)	51.5	36.1	12.8	1.387	1.218	1697	188
Aubé (2-17)	43.2	33.8	16.3	1.363	1.234	1685	185
2-155c	41.8	36.8	16.1	1.378	1.221	1670	184.3

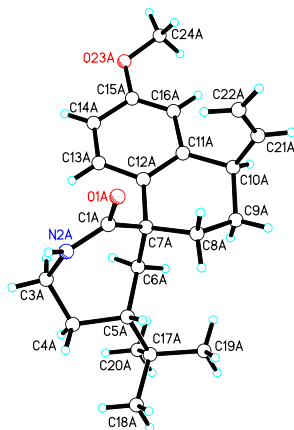


Figure 102. ORTEP representation (partial data) of amide **2-155e**.

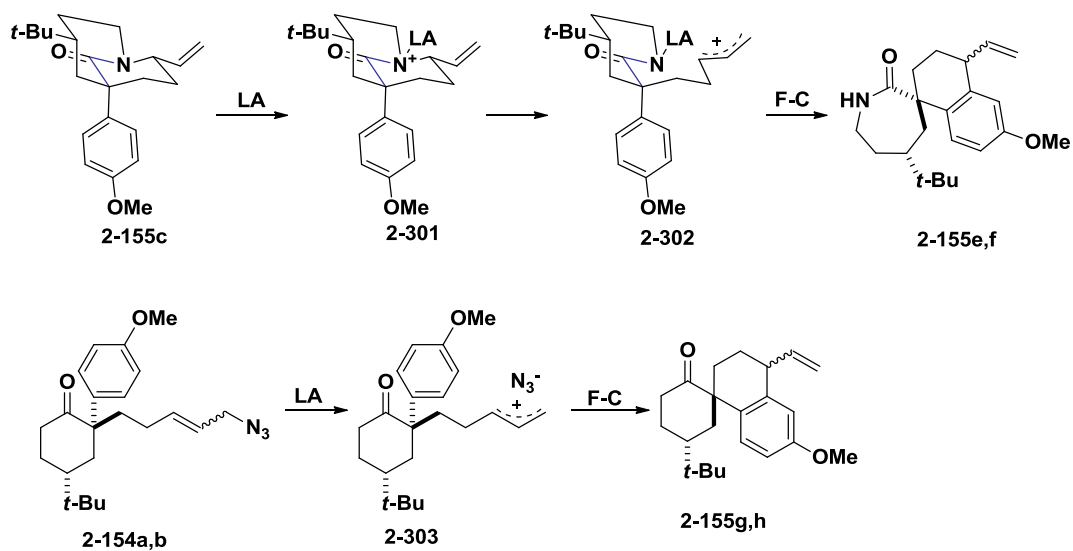
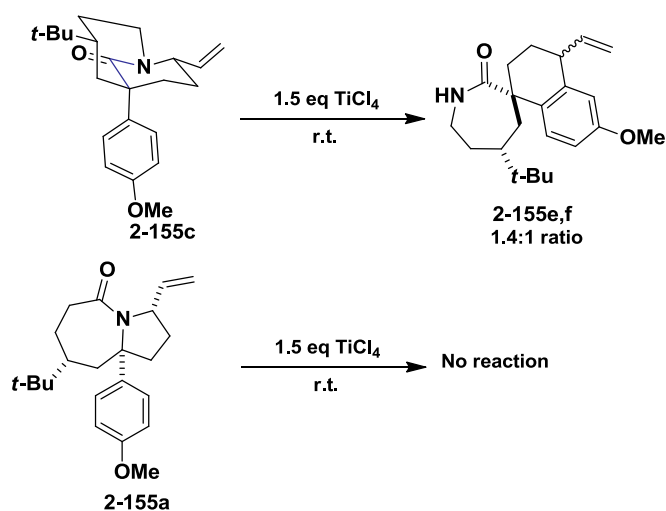


Figure 103. Proposed mechanism leading to **2-155e,f** and **2-155g,h**.

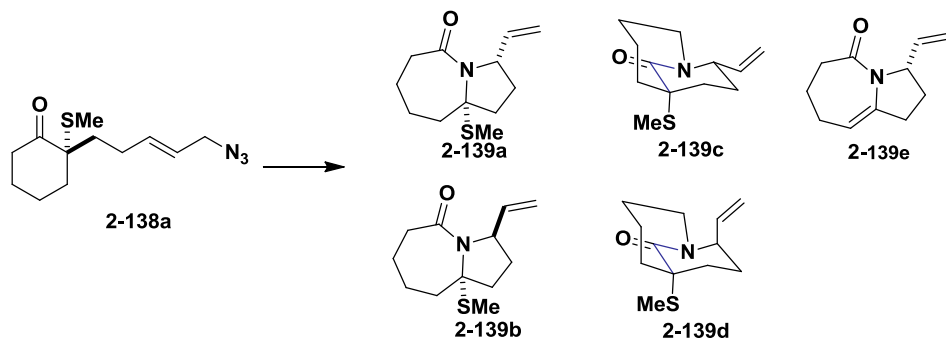
The formation of bicyclic amides **2-155e** and **2-155f** further confirmed the proposed mechanism; however, no reaction occurred for traditional fused amide **2-155a** under the same condition (Scheme 70).



Scheme 70. Friedel-Crafts reaction of twisted amide.

Methyl sulfide group was reported to have good cation- n intereaction capability, which can be utilized to produce twisted amides.⁷³ When azides **2-138** were treated with TiCl_4 , only lactam **2-139e** was obtained in 12% yield, without any twisted amide (Table 39). Its formation is supposed to be from the elimination of methyl sulfide group of normal amide **2-139a** (Figure 104). Twisted amide **2-139c** was obtained in 7% yield, along with 10% of **2-139e**, when treating with MeAlCl_2 .

Table 39. Condition-screening for allylic azides **2-138**.

			
	Condition	Yield	Ratio
1	1.5 eq TiCl ₄ , DCE, reflux	12% (2-139e)	
2	1.5 eq MeAlCl ₂ , DCE, reflux	7% (2-139c) 10% (2-139e)	1.1:1 (c:e)

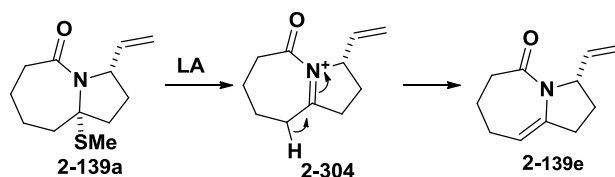
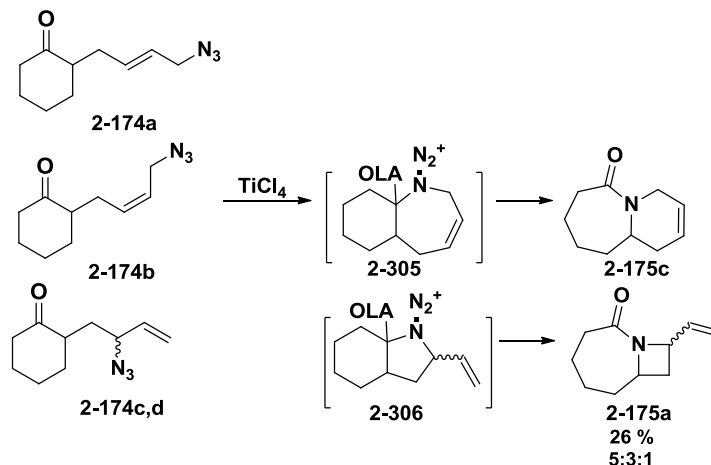


Figure 104. The elimination of lactam **2-139a** to **2-139e**.

2.11 The combination of allylic azide rearrangement and 2C Schmidt reaction

With the successful experience of the combination of allylic azide rearrangement and 3C intramolecular Schmidt reaction, we tried to know the result of this combination on a 2C Schmidt reaction (Scheme 71). When treating azides **2-174** with TiCl₄, a mixture of lactams

2-175c, and **2-175a** (two isomers) was obtained with 5:3:1 ratio. This confirmed the possibility of the combination on 2C Schmidt substrate.



Scheme 71. The combination with one carbon-less side chain.

However, when more substrates were tested on this combination, no positive results were obtained; the azides were either nor reactive or decomposed under the tested conditions (Figure 105).

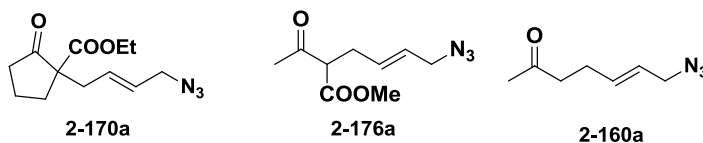
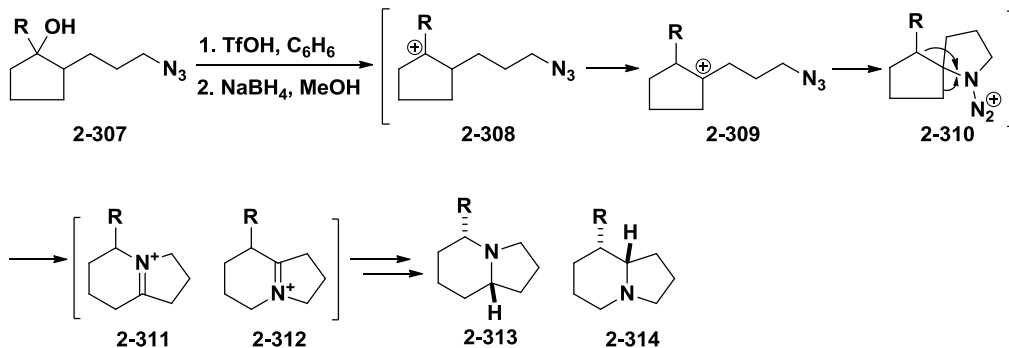


Figure 105. More 2C Schmidt substrates on the combination.

2.12 The combination of allylic azide rearrangement and carbocation-mediated Schmidt reaction

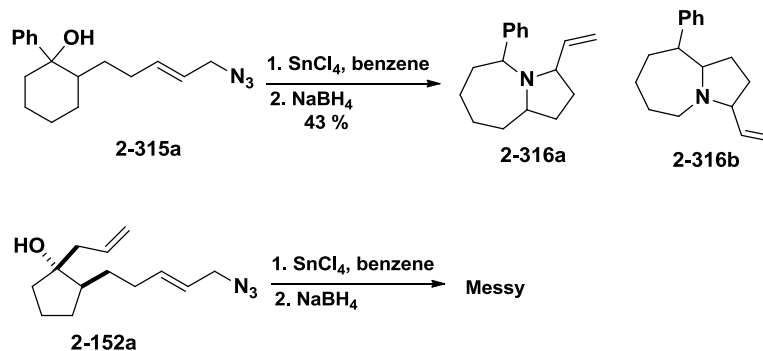
Pearson and coworkers reported the carbocation-mediated Schmidt reaction,¹⁰⁴ in which carbocations such as **2-308**, generated from alcohol **2-307** or olefin (not shown) under the activation of Lewis acid, undergo migration to carbocation **2-309** in order to facilitate the next five-membered ring closure to **2-310**. Two possible bond migrations provide two

iminium ion intermediates **2-311** and **2-312**; and the following reduction provides bicycle **2-313** and **2-314**.



Scheme 72. Carbocation-mediated intramolecular Schmidt reaction.

We speculated if allylic azides can undergo the similar transformations to generate disubstituted bicycles. Azides **2-315** were tested for this combination to afford a mixture of compounds **2-316a** and **2-316b** in 30% yield, whose ratio was not determined due to the existence of many possible isomers (Scheme 73). However, azides **2-152** did not provide any positive results.



Scheme 73. Carbocation-mediated Schmidt reaction of allylic azides.

2.13 Conclusion

In this chapter, the combination of allylic azide rearrangement and intramolecular Schmidt reaction was reported and its stereocontrol results were discussed.

Isomeric allylic azides were prepared by two methods: allylic bromination-azide displacement, and one- or two-pot cross-metathesis-azide displacement. Most of γ - and δ -substituted allylic azides contain 48–67% of trans isomer, 5–13% of cis isomer, and 24–44% of internal isomer. Trans and internal isomers can be obtained after careful column isolation. Their ratio changes were studied based on the substrate, time, temperature and Lewis acid.

Only 1.2:1 ratio was obtained for azide **2-65** in the combination of allylic azide rearrangement and intramolecular Schmidt reaction; which was below our expectation. Conformational analysis and computational calculation assisted in deeply understanding its mechanism. The next step was to study the impact of substituents of the cyclohexanone on the stereocontrol. High diastereoselectivity was obtained from azides **2-130**, **2-140** and **2-142**. For azide **2-130**, the side chain was forced to the axial position due to the equatorial bulky *t*-butyl group. This resulted in the formation of only one stable intermediate **2-240**. For azides **2-140** and **2-142**, the boat-conformation intermediates were generated to afford lactams with high dr. Dihedral angle between side chain and ketone was used to rationalize the diastereoselectivity of different substrates in the combination.

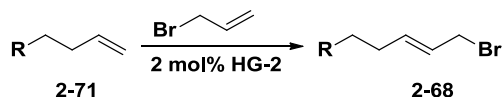
Carbocation-mediated allylic azide rearrangement was discovered when phenyl-substituted allylic azides were used in this combination. It was further confirmed using the known allylic azides.

The Prins reaction is the major side reactions in this combination. Most Prins adducts were generated when treating allylic azides with TiCl_4 , which are usually not obtained from SnCl_4 .

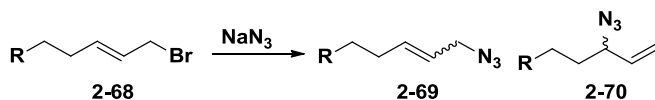
During the preparation of twisted amide from this combination, allylic twisted amide can undergo further Friedel-Crafts reaction when treating allylic azides with more than 1 equivalent of Lewis acid.

Initial studies were conducted for the combination of allylic azide rearrangement and 2C or carbocation Schmidt reaction.

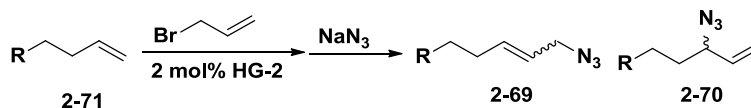
2.14 Experimental data



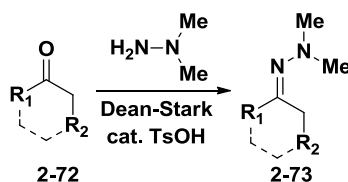
General procedure I: To a solution of Hoveyda-Grubbs catalyst 2nd generation (HG-2, 0.16 mmol) in dichloromethane (12 mL) under N₂ atmosphere at room temperature was added a solution of olefin **2-71** (6.3 mmol) and allyl bromide (15 – 30 mmol) in dichloromethane (5 mL) slowly. The reaction mixture was stirred overnight. The solvent was concentrated in vacuum and the residue was purified by chromatography to afford colorless oil bromide **2-68**.



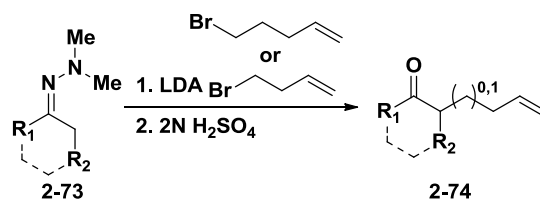
General procedure II: A suspension of bromides **2-68** (1.1 mmol) and sodium azide (3.3 mmol) in DMF (6 mL) at room temperature was stirred overnight. Diethyl ether and water were added and the aqueous layer was washed three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography to afford a mixture of azides **2-69** and **2-70**.



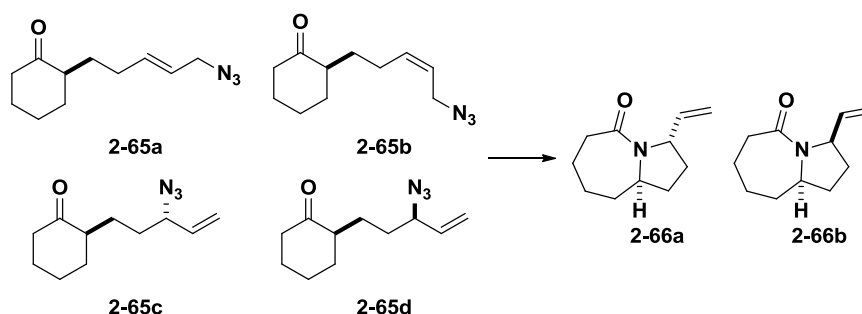
General procedure III: To a solution of Hoveyda-Grubbs 2nd generation catalyst (HG-2, 0.450 mmol) in dichloromethane (20 mL) under N₂ atmosphere at room temperature was slowly added a solution of olefin **2-71** (8.9 mmol) and allyl bromide (45 mmol) in dichloromethane (10 mL). The resulting reaction mixture was stirred overnight (as specified). The solvent was concentrated in vacuum and the residue was dissolved in DMSO (10 mL) and DMF (20 mL), followed by the addition of sodium azide (50.0 mmol) at room temperature. After being allowed to stir overnight, diethyl ether and water were added and the aqueous layer was washed three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography to afford a mixture of azides **2-69** and **2-70**.



General procedure IV: A solution of ketone **2-72** (46 mmol), 1,1-dimethylhydrazine (150 mmol), and *p*-toluenesulfonic acid monohydrate (2.0 mmol) in benzene (70 mL) was refluxed using a Dean-Stark apparatus for 20 h. The reaction was cooled to rt, and the solvent was removed in vacuum. Diethyl ether and saturated aqueous sodium bicarbonate were added and the aqueous layer was washed three times with diethyl ether. The combined organic layers were washed with saturated aqueous sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. The concentration afforded hydrazone **2-73**, which was usually used directly in the next step without further purification.

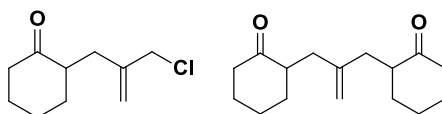


General procedure V: To a solution of diisopropylamine (4.33 g, 42.8 mmol) in anhydrous THF (50 mL) under N₂ atmosphere at 0 °C was slowly added n-BuLi (16.4 mL, 2.4 M in hexane, 39.3 mmol). The ice bath was removed after 10 min and the reaction stirred for another 20 min. The reaction mixture was cooled to 0 °C and ketone dimethylhydrazone (35.7 mmol) was slowly added. After the addition, the ice bath was removed and the reaction stirred for another 3 h. The reaction mixture was cooled to 0 °C, bromide (42.8 mmol) was slowly added, and the resulting mixture was stirred overnight. The solution was poured into a mixture of cold 2 M H₂SO₄ solution (80 mL) and diethyl ether (80 mL), and was vigorously stirred for 1 h at room temperature. After separation, the aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography to afford **2-74**.



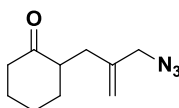
General procedure VI: To a refluxing solution of azides **2-65a**, **2-65b**, **2-65c** and **2-65d** (0.57 mmol) in anhydrous dichloromethane (8 mL) under N₂ atmosphere was added tin

tetrachloride (0.86 mmol). After refluxing for 15 h, saturated aqueous ammonium chloride was added to the cooled reaction mixture. After separation, the aqueous layer was washed with dichloromethane. The aqueous layer was neutralized by saturated aqueous sodium bicarbonate, and washed twice with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography to afford lactams **2-66a** and **2-66b**.



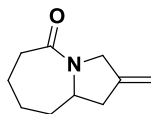
2-(2-(Chloromethyl)allyl)cyclohexanone and **2,2'-(2-methylenepropane-1,3-diyl)dicyclohexanone**. According to the general procedure **V**, cyclohexanone dimethylhydrazone (5.00 g, 35.7 mmol) and 3-chloro-2-chloromethyl-1-propene (5.35 g, 42.8 mmol) afforded 2-(2-(chloromethyl)allyl)cyclohexanone (1.10 g, 17%) as a colorless oil and 2,2'-(2-methylenepropane-1,3-diyl)dicyclohexanone (colorless oil, 0.72 g, 16% and white solid, 0.95 g, 21%) after chromatography (1-30% EtOAc/hexanes). 2-(2-(Chloromethyl)allyl)cyclohexanone: R_f = 0.35 (20% EtOAc/hexanes); IR (neat) 2937, 1710, 1148 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.34-1.43 (m, 1H), 1.65-1.75 (m, 2H), 1.86-1.93 (m, 1H), 2.03-2.20 (m, 3H), 2.31-2.38 (m, 1H), 2.41-2.48 (m, 1H), 2.53-2.62 (m, 1H), 2.75 (dd, J = 5.6 Hz, 14.8 Hz, 1H), 4.05 (s, 2H), 4.95 (q, J = 1.2 Hz, 1H), 5.20 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.0 (CH_2), 28.1 (CH_2), 33.2 (CH_2), 33.9 (CH_2), 42.1 (CH_2), 48.4 (CH_2), 48.8 (CH), 116.1 (CH_2), 143.0 (C), 212.2 (C). 2,2'-(2-Methylenepropane-1,3-diyl)dicyclohexanone (colorless oil): IR (neat): 2934, 1709, 1128, 886 cm^{-1} ; HRMS (ESI) m/z calculated for

(M+H)⁺ (C₁₆H₂₅O₂) 249.1855, found: 249.1864; ¹H NMR (400 MHz, CDCl₃) δ 1.27-1.34 (m, 2H), 1.65-1.73 (m, 4H), 1.78-1.89 (m, 4H), 2.06-2.11 (m, 2H), 2.13-2.19 (m, 2H), 2.30-2.43 (m, 4H), 2.52-2.58 (m, 4H), 4.74 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 25.0 (CH₂), 28.1 (CH₂), 33.8 (CH₂), 35.8 (CH₂), 42.1 (CH₂), 48.7 (CH), 111.6 (CH₂), 145.0 (C), 212.8 (C).
 2,2'-(2-Methylenepropane-1,3-diyl)dicyclohexanone (white solid): IR (neat): 2937, 1699, 1130, 901 cm⁻¹; HRMS (ESI) m/z calculated for (M+Na)⁺ (C₁₆H₂₄O₂Na) 271.1674, found: 271.1635; ¹H NMR (400 MHz, CDCl₃) δ 1.21-1.31 (m, 2H), 1.62-1.68 (m, 4H), 1.82-1.88 (m, 4H), 2.06-2.16 (m, 4H), 2.29-2.38 (m, 2H), 2.38-2.45 (m, 4H), 2.56 (dd, *J* = 4.0 Hz, 14.8 Hz, 2H), 4.76 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 25.0 (CH₂), 28.0 (CH₂), 33.2 (CH₂), 34.9 (CH₂), 42.1 (CH₂), 48.0 (CH), 113.5 (CH₂), 144.4 (C), 212.8 (C).

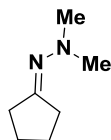


2-(2-(Azidomethyl)allyl)cyclohexanone (2-200). A suspension of 2-(2-(chloromethyl)allyl)cyclohexanone (1.10 g, 5.90 mmol), sodium azide (1.15 g, 17.7 mmol), and sodium iodide (44 mg, 0.30 mmol) in DMF (10 mL) was stirred overnight at room temperature. Diethyl ether and water were added and the aqueous layer was washed three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography (0.5-8% EtOAc/hexanes) to afford **2-200** (1.0 g, 89%) as a colorless oil. *R_f* = 0.5 (20% EtOAc/hexanes); IR (neat) 2937, 2100, 1710 cm⁻¹; HRMS (ESI) m/z calculated for (C₁₀H₁₅N₃O+Na)⁺ 216.1113, found: 216.1148; ¹H NMR (400 MHz, CDCl₃) δ 1.31-1.41 (m, 1H), 1.63-1.75 (m, 2H), 1.84-1.93 (m, 1H), 2.06 (dd, *J* = 7.6 Hz, 14.8 Hz, 1H), 2.04-2.18 (m, 2H), 2.30-2.39 (m, 1H), 2.40-2.47 (m, 1H), 2.49-2.56 (m, 1H), 2.65 (dd, *J* = 6.0 Hz, 14.8 Hz,

1H), 3.47 (dd, J = 14.0 Hz, 18.4 Hz, 2H), 4.97 (s, 1H), 5.10 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.0 (CH_2), 28.0 (CH_2), 33.7 (CH_2), 33.9 (CH_2), 42.1 (CH_2), 48.8 (CH), 56.2 (CH_2), 115.1 (CH), 141.3 (C), 212.0 (C).

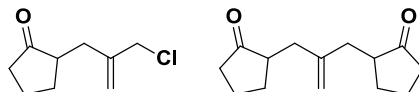


2-Methylene-hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (2-201). According to the general procedure **VI**, azide **2-200** (0.11 g, 0.57 mmol) and tin tetrachloride (0.86 mL, 1 M in dichloromethane, 0.86 mmol) afforded lactam **2-201** (78 mg, 83%) as a colorless oil after column chromatography (1-75% EtOAc/hexanes). Lactam **2-201**: R_f = 0.40 (100% EtOAc/hexanes); IR (neat) 2930, 1626, 1445 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{10}\text{H}_{16}\text{NO}+\text{H})^+$ 166.1232, found: 166.1227; ^1H NMR (400 MHz, CDCl_3) δ 1.45-1.58 (m, 3H), 1.76-1.97 (m, 3H), 2.35 (dd, J = 3.6 Hz, 15.6 Hz, 1H), 2.43 (dd, J = 11.6 Hz, 12.8 Hz, 1H), 2.54 (dd, J = 6.8 Hz, 14.0 Hz, 1H), 2.93 (dd, J = 8.8 Hz, 14.4 Hz, 1H), 3.88 (sextet, J = 5.6 Hz, 1H), 4.10 (dd, J = 16.0 Hz, 38.8 Hz, 2H), 4.96 (q, J = 1.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.3 (CH_2), 29.6 (CH_2), 35.9 (CH_2), 37.8 (CH_2), 40.8 (CH_2), 51.5 (CH_2), 59.0 (CH), 107.1 (CH_2), 143.0 (C), 174.2 (C).

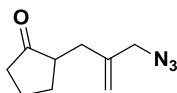


2-Cyclopentylidene-1,1-dimethylhydrazine.¹⁰⁵ According to the general procedure **IV**, cyclopentanone (26.5 mL, 0.30 mol) and 1,1-dimethylhydrazine (45.6 mL, 0.60 mmol) afforded 2-cyclopentylidene-1,1-dimethylhydrazine (24.9 g, 66%) as a colorless oil. ^1H NMR

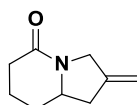
(400 MHz, CDCl₃) δ 1.68-1.77 (m, 4H), 2.31-2.39 (m, 4H), 2.45 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 24.1 (CH₂), 24.9 (CH₂), 29.3 (CH₂), 33.5 (CH₂), 47.0 (CH₃), 175.8 (C).



2-(2-(Chloromethyl)allyl)cyclopentanone and 2,2'-(2-methylenepropane-1,3-diyl)dicyclopentanone. According to the general procedure V, 2-cyclopentylidene-1,1-dimethylhydrazine (5.04 g, 40.0 mmol) and 3-chloro-2-chloromethyl-1-propene (6.0 g, 48.0 mmol) afforded 2-(2-(chloromethyl)allyl)cyclopentanone (colorless oil, 280 mg, 4%) and 2,2'-(2-methylenepropane-1,3-diyl)dicyclopentanone (two isomers with ratio 2:3, colorless oil, 190 mg, 9%) after column chromatography (1-30% EtOAc/hexanes). 2-(2-(Chloromethyl)allyl)cyclopentanone: R_f = 0.55 (20% EtOAc/hexanes); IR (neat): 2963, 1738, 1155 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.48-1.58 (m, 1H), 1.73-1.87 (m, 1H), 2.01-2.38 (m, 6H), 2.72 (dd, J = 3.6 Hz, 14.8 Hz, 1H), 4.05 (s, 2H), 5.00 (s, 1H), 5.20 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.5 (CH₂), 29.7 (CH₂), 33.6 (CH₂), 37.9 (CH₂), 47.4 (CH), 48.0 (CH₂), 115.9 (CH₂), 143.1 (C), 220.0 (C). 2,2'-(2-methylenepropane-1,3-diyl)dicyclopentanone (colorless oil): R_f = 0.25 (20% EtOAc/hexanes); IR (neat): 2962, 1736, 1156 cm⁻¹; HRMS (ESI) m/z calculated for C₁₄H₂₀O₂Na (M+Na)⁺ 243.1361, found: 243.1353; ¹H NMR (400 MHz, CDCl₃) δ 1.43-1.54 (m, 2H), 1.73-1.90 (m, 4H), 1.98-2.04 (m, 2H), 2.08-2.36 (m, 8H), 2.54 (t, J = 14.4 Hz, 2H), 4.78-4.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 20.5 (CH₂), 20.6 (CH₂), 29.4 (CH₂), 29.7 (CH₂), 35.6 (CH₂), 36.2 (CH₂), 37.95 (CH₂), 38.04 (CH₂), 47.2 (CH), 47.6 (CH), 111.8 (CH₂), 112.8 (CH₂), 144.9 (C), 145.2 (C), 220.7 (C), 220.8 (C).

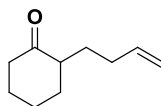


2-(2-(Azidomethyl)allyl)cyclopentanone (2-203). A suspension of 2-(2-(chloromethyl)allyl)cyclopentanone (280 mg, 1.63 mmol), sodium azide (325 mg, 4.9 mmol) and sodium iodide (30 mg, 0.2 mmol) in DMF (3 mL) at room temperature was stirred overnight. Diethyl ether and water were added and the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The concentration afforded a residue, which was purified by column chromatography (1-3% EtOAc/hexanes) to afford azide **2-203** (202 mg, 69%) as a colorless oil. Azide **2-203**: R_f = 0.45 (20% EtOAc/hexanes); IR (neat): 2962, 2100, 1739 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.50-1.60 (m, 1H), 1.77-1.88 (m, 1H), 1.96-2.04 (m, 2H), 2.10-2.40 (m, 4H), 2.63 (dd, J = 2.8 Hz, 14.8 Hz, 1H), 3.76 (dd, J = 2.0 Hz, 16.8 Hz, 2H), 5.04 (s, 1H), 5.12 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5 (CH_2), 29.7 (CH_2), 34.2 (CH_2), 37.9 (CH_2), 47.5 (CH), 55.9 (CH_2), 115.1 (CH_2), 141.3 (C), 220.0 (C).

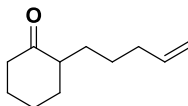


2-Methylenehexahydroindolizin-5(1H)-one (2-204). According to the general procedure **VI**, azide **2-203** (74 mg, 0.41 mmol) and tin tetrachloride (0.62 mL, 1 M in dichloromethane, 0.62 mmol) afforded lactam **2-204** (15 mg, 24%) as a colorless oil after column chromatography (15-75% EtOAc/hexanes). Lactam **2-204**: R_f = 0.15 (20% EtOAc/hexanes); IR (neat): 2924, 1625, 1451 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_9\text{H}_{13}\text{NONa}$ ($\text{M}+\text{Na}$) $^+$ 174.0895, found: 174.0909; ^1H NMR (400 MHz, CDCl_3) δ 1.34-1.44 (m, 1H), 1.67-1.80 (m, 1H), 1.95-2.01 (m, 1H), 2.13-2.18 (m, 1H), 2.28-2.37 (m, 2H), 2.48

(dd, $J = 6.4$ Hz, 18 Hz, 1H), 2.69 (ddd, $J = 1.2$ Hz, 5.6 Hz, 14.8 Hz, 1H), 3.57-3.63 (m, 1H), 3.88 (d, $J = 16.8$ Hz, 1H), 4.43 (d, $J = 16.8$ Hz, 1H), 5.03-5.06 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9 (CH_2), 29.4 (CH_2), 31.0 (CH_2), 40.8 (CH_2), 49.5 (CH_2), 59.2 (CH), 107.5 (CH_2), 142.9 (C), 168.6 (C).

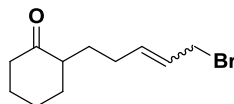


2-(But-3-enyl)cyclohexanone.¹⁰⁶ According to the general procedure V, the reaction of 2-cyclohexylidene-1,1-dimethylhydrazine (5.0 g, 36 mmol) afforded the title ketone 2-(but-3-enyl)cyclohexanone (5.2 g, 96%) as a colorless oil. $R_f = 0.70$ (20% EtOAc/hexanes); IR (neat): 2935, 1710, 1449 cm^{-1} ; HRMS (EI) m/z calculated for $(\text{C}_{10}\text{H}_{16}\text{O})^+$ 152.1201, found: 152.1189; ^1H NMR (400 MHz, CDCl_3) δ 1.23-1.32 (m, 1H), 1.34-1.44 (m, 1H), 1.62-1.73 (m, 2H), 1.82-1.97 (m, 2H), 2.03-2.14 (m, 4H), 2.28-2.33 (m, 2H), 2.37-2.42 (m, 1H), 4.94-5.04 (m, 2H), 5.74-5.84 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.0 (CH_2), 28.0 (CH_2), 28.5 (CH_2), 31.2 (CH_2), 33.9 (CH_2), 42.1 (CH_2), 49.8 (CH), 114.7 (CH_2), 138.5 (CH), 213.2 (C).

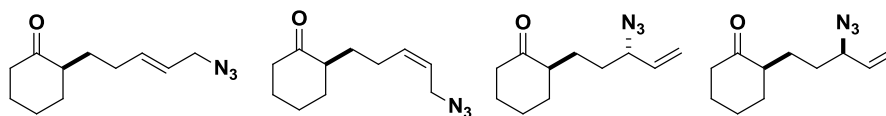


2-(Pent-4-en-1-yl)cyclohexanone. According to the general procedure V, 2-cyclohexylidene-1,1-dimethylhydrazine (7.0 g, 50 mmol) and 5-bromo-1-pentene (10.6 g, 65.0 mmol) afforded the title ketone 2-(pent-4-en-1-yl)cyclohexanone (8.7 g, 100%) as a colorless oil after column chromatography (3% EtOAc/hexanes). $R_f = 0.65$ (20% EtOAc/hexanes); IR (neat): 2933 1711, 1449, 1127 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.14-1.23 (m, 1H), 1.31-1.42 (m, 3H), 1.60-1.69 (m, 2H), 1.72-1.85 (m, 2H), 2.00-2.11 (m, 4H), 2.24-2.29 (m, 2H), 2.35-2.41 (m, 1H), 4.92-5.01 (m, 2H), 5.74-5.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ

24.9 (CH₂), 26.5 (CH₂), 28.0 (CH₂), 28.9 (CH₂), 33.86 (CH₂), 33.88 (CH₂), 42.0 (CH₂), 50.6 (CH), 114.4 (CH₂), 138.7 (CH), 213.3 (C).

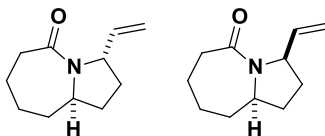


2-(5-Bromopent-3-enyl)cyclohexanone. According to the general procedure I, 2-(but-3-enyl)cyclohexanone (0.61 g, 4.0 mmol), HG-2 (50 mg, 0.080 mmol, 2 mol%) and allyl bromide (0.68 mL, 8.0 mmol) afforded a mixture of the title bromide 2-(5-bromopent-3-enyl)cyclohexanone (320 mg, 33%, E/Z: 5:1 ratio) as colorless oil after column chromatography (3% EtOAc/hexanes). R_f = 0.50 (20% EtOAc/hexanes); IR (neat): 2934, 1709, 1448 cm⁻¹. E isomer: ¹H NMR (400 MHz, CDCl₃) δ 1.25-1.32 (m, 1H), 1.34-1.43 (m, 1H), 1.64-1.72 (m, 2H), 1.85-1.96 (m, 2H), 2.04-2.14 (m, 4H), 2.26-2.42 (m, 3H), 3.96 (d, J = 6.4 Hz, 2H), 5.68-5.78 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 25.0 (CH₂), 28.0 (CH₂), 28.4 (CH₂), 29.6 (CH₂), 33.4 (CH₂), 34.0 (CH₂), 42.1 (CH₂), 49.8 (CH), 126.7 (CH), 136.1 (CH), 213.0 (C). Z isomer (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) 4.00 (d, J = 8.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 25.0 (CH₂), 28.1 (CH₂), 34.2 (CH₂), 125.9 (CH), 135.4 (CH), 213.1 (C).



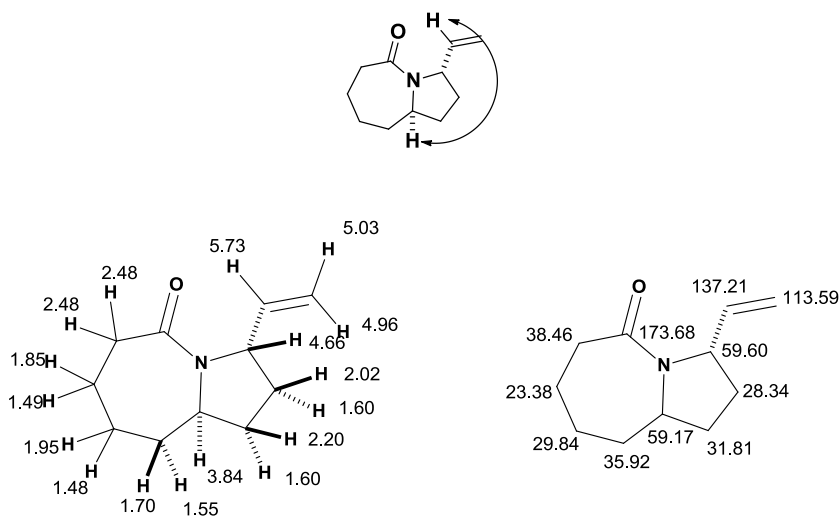
(2*R,*E*)-2-(5-Azidopent-3-enyl)cyclohexanone (2-65a), (2*R**,*Z*)-2-(5-azidopent-3-enyl)cyclohexanone (2-65b), (2*R**)-2-(3'*S*')-3-azidopent-4-enylcyclohexanone (2-65c), and (2*R**)-2-(3'*R*')-3-azidopent-4-enylcyclohexanone (2-65d).** According to the general procedure II, 2-(5-bromopent-3-enyl)cyclohexanone (0.27 g, 1.1 mmol) and sodium azide

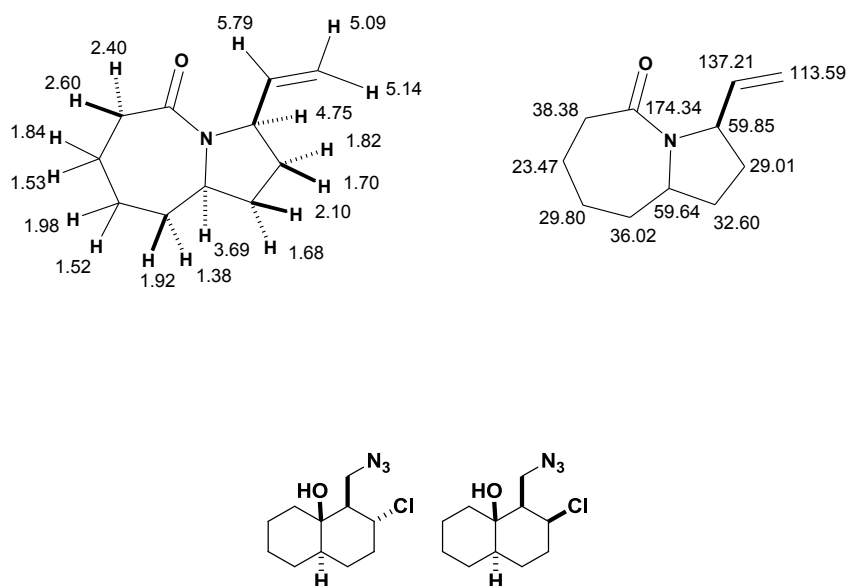
(0.22 g, 3.3 mmol) afforded a mixture of azides **2-65a**, **2-65b**, **2-65c**, and **2-65d** (225 mg, 99%, 62:8:15:15 ratio from ^1H NMR in acetone; 64:6:15:15 from ^1H NMR in CDCl_3) as a colorless oil after chromatography (1-5% EtOAc/hexanes). Azides **2-65a**, **2-65b**, **2-65c**, and **2-65d**: R_f = 0.50 (20% EtOAc/hexanes); IR (neat): 2935, 2098, 1709 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{22}\text{H}_{34}\text{N}_4\text{O}_2+\text{H})^+$ 387.2760 (corresponding to $(2\text{M}-\text{N}_2+\text{H})^+$), found: 387.2719. Azide **2-65a**: ^1H NMR (400 MHz, acetone) δ 1.19-1.30 (m, 1H), 1.30-1.41 (m, 1H), 1.53-1.78 (m, 3H), 1.82-1.90 (m, 2H), 2.03-2.16 (m, 3H), 2.25-2.28 (m, 1H), 2.31-2.42 (m, 2H), 3.77 (d, J = 6.4 Hz, 2H), 5.55-5.62 (m, 1H), 5.76-5.86 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 24.8 (CH_2), 27.8 (CH_2), 28.8 (CH_2), 29.6 (CH_2), 33.8 (CH_2), 41.6 (CH_2), 49.3 (CH), 52.3 (CH_2), 123.33 (CH), 136.5 (CH), 210.9 (C). Azide **2-65b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.89 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, acetone) δ 49.4 (CH), 122.5 (CH), 135.7 (CH), 211.0 (C). Azides **2-65c** and **2-65d** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.97 (q, J = 7.2 Hz, 1H), 5.27-5.36 (m, 2H), 5.76-5.86 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 25.7 (CH_2), 25.8 (CH_2), 31.6 (CH_2), 31.7 (CH_2), 49.7 (CH), 49.7 (CH), 65.0 (CH), 65.1 (CH), 117.49 (CH_2), 117.51 (CH_2), 136.12 (CH), 136.16 (CH), 210.82 (C), 210.84 (C).



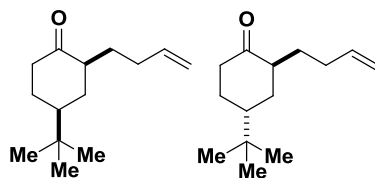
(**3S*,9aR***)-3-Vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-66a**) and (**3R*,9aR***)-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-66b**). According to the general procedure **VI**, azides **2-65a**, **2-65b**, **2-65c**, and **2-65d** (500 mg, 2.41 mmol) and tin tetrachloride (3.8 mL, 1 M in dichloromethane, 3.8 mmol) afforded lactam **2-66a** (161 mg, 37%) as a colorless oil and **2-66b** (134 mg, 31%) as a colorless oil after column

chromatography (10-100% EtOAc/hexanes). Lactam **2-66a**: R_f = 0.7 (100% EtOAc, twice); IR (neat): 2928, 1635, 1447, 1415 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{11}\text{H}_{17}\text{NO}+\text{H})^+$ 180.1388, found: 180.1380; ^1H NMR (400 MHz, CDCl_3) δ 1.45-1.68 (m, 6H), 1.79-1.83 (m, 1H), 1.92-1.97 (m, 1H), 1.97-2.04 (m, 1H), 2.19-2.24 (m, 1H), 2.47-2.50 (m, 2H), 3.83 (t, J = 9.2 Hz, 1H), 4.66 (dd, J = 5.6 Hz, 6.8 Hz, 1H), 4.95-5.05 (m, 2H), 5.69-5.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.4 (CH_2), 28.3 (CH_2), 29.8 (CH_2), 31.8 (CH_2), 35.9 (CH_2), 38.5 (CH_2), 59.2 (CH), 59.6 (CH), 113.6 (CH_2), 137.2 (CH), 173.7 (C). Lactam **2-66b**: R_f = 0.65 (100% EtOAc, twice); IR (neat): 2927, 1636, 1446 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{11}\text{H}_{17}\text{NO}+\text{H})^+$ 180.1388, found: 180.1376; ^1H NMR (400 MHz, CDCl_3) δ 1.35-1.46 (m, 1H), 1.47-1.55 (m, 2H), 1.68-1.75 (m, 2H), 1.79-1.97 (m, 4H), 2.08-2.13 (m, 1H), 2.41 (dd, J = 12.0 Hz, 14.0 Hz, 1H), 2.59 (dd, J = 7.2 Hz, 14.4 Hz, 1H), 3.69 (dd, J = 9.2 Hz, 16.4 Hz, 1H), 4.75 (t, J = 6.0 Hz, 1H), 5.08-5.16 (m, 2H), 5.75-5.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.5 (CH_2), 29.0 (CH_2), 29.8 (CH_2), 32.6 (CH_2), 36.0 (CH_2), 38.4 (CH_2), 59.6 (CH), 59.9 (CH), 114.2 (CH_2), 137.9 (CH), 174.3 (C). The following data and NOE correlations were used to assign lactams **2-66a** and **2-66b**.

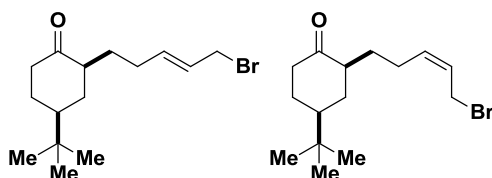




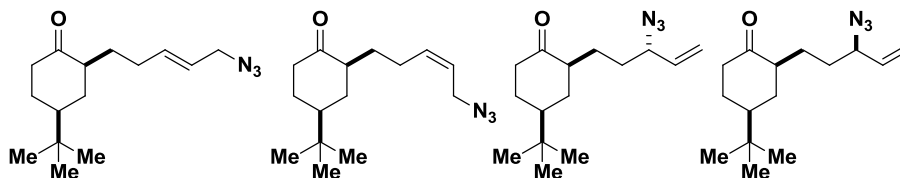
(**3R*,4R*,4aR*,8aR***)-4-(Azidomethyl)-3-chlorodecahydronaphthalen-4a-ol (**2-66f**) and (**3S*,4R*,4aR*,8aR***)-4-(azidomethyl)-3-chlorodecahydronaphthalen-4a-ol (**2-66g**). According to the general procedure **VI**, azides **2-65a**, **2-65b**, **2-65c**, and **2-65d** (75 mg, 0.36 mmol) and titanium tetrachloride (0.54 mL, 1 M in dichloromethane, 0.54 mmol) afforded lactam **2-66a** (7 mg, 11%) as a colorless oil, **2-66b** (8 mg, 12%) as a colorless oil, and a mixture of alcohols **66f** and **66g** (5:2 ratio, 14 mg, 16%) after column chromatography (1-100% EtOAc/hexanes). Alcohol **66f**: R_f = 0.55 (20% EtOAc, twice); ^1H NMR (400 MHz, CDCl_3) δ 1.21-1.30 (m, 3H), 1.31-1.42 (m, 3H), 1.49-1.56 (m, 2H), 1.57-1.67 (m, 2H), 1.67-1.84 (m, 2H), 1.87-1.96 (m, 1H), 2.30 (d, J = 1.0 Hz, 1H), 2.37 (dq, J = 11.0, 3.4 Hz, 1H), 3.85 (dd, J = 13.0, 2.5 Hz, 1H), 4.04 (dd, J = 13.0, 3.2 Hz, 1H), 4.37 (td, J = 11.4, 4.6 Hz, 1H). Alcohol **66g** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 2.25 (dq, J = 14.5, 3.0 Hz, 1H), 2.53 (d, J = 2.5 Hz, 1H), 3.69 (dd, J = 12.4, 10.2 Hz, 1H), 3.80 (dd, J = 12.4, 4.7 Hz, 1H), 4.69 (q, J = 2.9 Hz, 1H).



(2*S,4*S**)-2-(But-3-enyl)-4-*tert*-butylcyclohexanone and (2*S**,4*R**)-2-(but-3-enyl)-4-*tert*-butylcyclohexanone.**¹⁰⁷ According to the general procedure V, 2-(4-(*tert*-butyl)cyclohexylidene)-1,1-dimethylhydrazine (7.85 g, 40.0 mmol) afforded (2*S**,4*S**)-2-(but-3-enyl)-4-*tert*-butylcyclohexanone (3.6 g, 43%) as a colorless oil and (2*S**,4*R**)-2-(but-3-enyl)-4-*tert*-butylcyclohexanone (3.5 g, 42%) as a colorless oil. (2*S**,4*S**)-2-(But-3-enyl)-4-*tert*-butylcyclohexanone: R_f = 0.45 (10% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 0.91 (s, 9H), 1.08-1.26 (m, 2H), 1.43 (dq, J = 4.8 Hz, 12.8 Hz, 1H), 1.58 (tt, J = 3.0 Hz, 12.0 Hz, 1H), 1.88-1.97 (m, 1H), 2.07-2.15 (m, 4H), 2.26-2.40 (m, 3H), 4.93-5.02 (m, 2H), 5.74-5.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 27.6 (3 CH_3), 28.4 (CH_2), 28.8 (CH_2), 31.3 (CH_2), 32.4 (C), 35.1 (CH_2), 41.7 (CH_2), 47.1 (CH), 48.8 (CH), 114.6 (CH_2), 138.6 (CH), 213.3 (C). (2*S**,4*R**)-2-(But-3-enyl)-4-*tert*-butylcyclohexanone: R_f = 0.4 (10% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 0.90 (s, 9H), 1.40-1.68 (m, 4H), 1.77-1.86 (m, 2H), 1.94-2.12 (m, 3H), 2.26-2.32 (m, 1H), 2.36-2.45 (m, 2H), 4.96-5.04 (m, 2H), 5.73-5.83 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.9 (CH_2), 27.4 (3 CH_3), 30.6 (CH_2), 31.3 (CH_2), 31.4 (CH_2), 32.4 (C), 38.4 (CH_2), 41.3 (CH_2), 48.5 (CH_2), 115.2 (CH_2), 137.8 (CH), 215.6 (C).

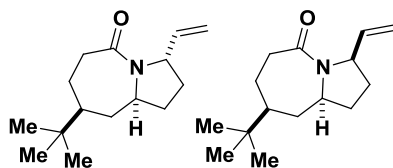


(2*S,4*S**,*E*)-2-(5-Bromopent-3-enyl)-4-*tert*-butylcyclohexanone** and **(2*S**,4*S**,*Z*)-2-(5-bromopent-3-enyl)-4-*tert*-butylcyclohexanone**. According to the procedure **I**, (2*S**,4*S**)-2-(but-3-enyl)-4-*tert*-butylcyclohexanone (2.38 g, 11.4 mmol) afforded a mixture of (2*S**,4*S**,*E*)-2-(5-bromopent-3-enyl)-4-*tert*-butylcyclohexanone and (2*S**,4*S**,*Z*)-2-(5-bromopent-3-enyl)-4-*tert*-butylcyclohexanone (1.3 g, 38%, *E*/*Z* 10:1 ratio) as a colorless oil. (2*S**,4*S**,*E*)-2-(5-Bromopent-3-enyl)-4-*tert*-butylcyclohexanone and (2*S**,4*S**,*Z*)-2-(5-bromopent-3-enyl)-4-*tert*-butylcyclohexanone: R_f = 0.30 (10% EtOAc/hexanes); IR (neat) 2954, 2868, 1712 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{30}\text{H}_{49}\text{BrO}_2+\text{Na})^+$ 543.2814 (corresponding to $(2\text{M-HBr}+\text{Na})^+$), found: 543.2808. *E* isomer: ^1H NMR (400 MHz, CDCl_3) δ 0.93 (s, 9H), 1.08-1.29 (m, 2H), 1.45 (dq, J = 4.8 Hz, 12.4 Hz, 1H), 1.60 (tt, J = 2.8 Hz, 12.0 Hz, 1H), 1.88-1.98 (m, 1H), 2.07-2.18 (m, 4H), 2.26-2.43 (m, 3H), 3.96 (d, J = 6.6 Hz, 1H), 5.66-5.80 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 27.7 (3 CH_3), 28.4 (CH_2), 28.8 (CH_2), 29.6 (CH_2), 32.5 (C), 33.5 (CH_2), 35.1 (CH_2), 41.7 (CH_2), 47.1 (CH), 48.8 (CH), 126.7 (CH), 136.2 (CH), 213.2 (C). *Z* isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) 4.00-4.03 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) 27.4 (3 CH_3).

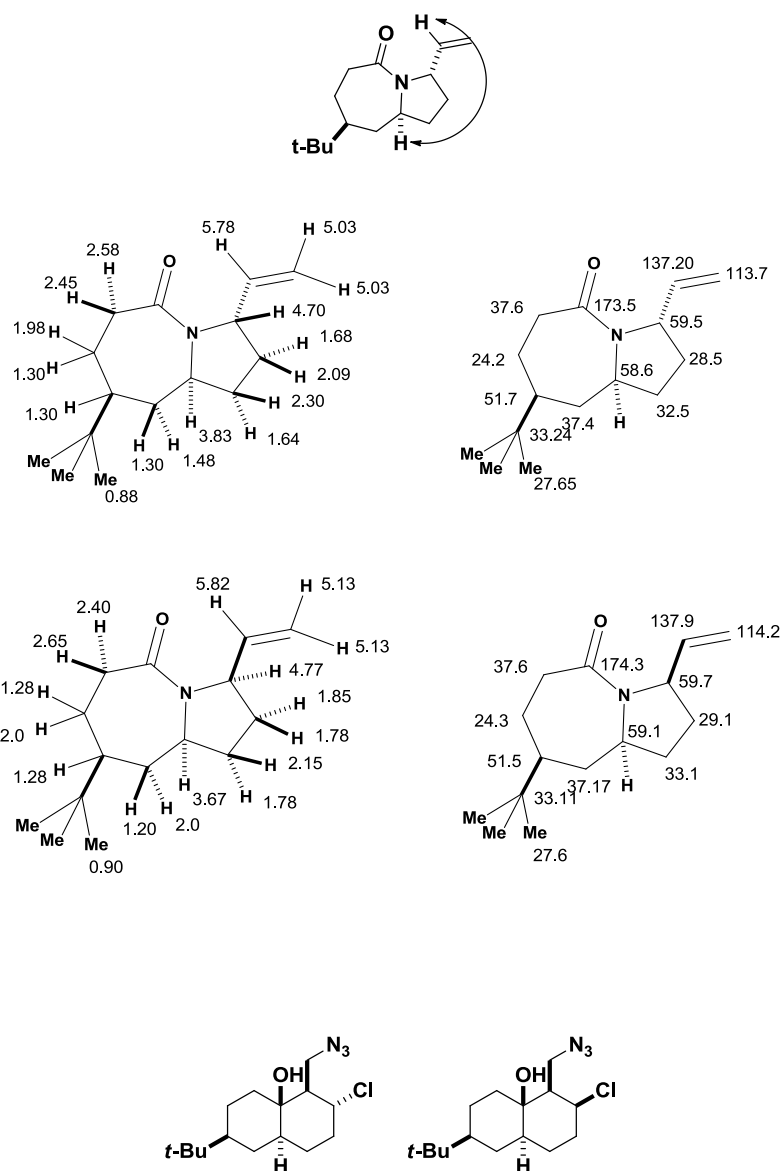


(2*S,4*S**,*E*)-2-(5-Azidopent-3-enyl)-4-*tert*-butylcyclohexanone** (2-128a),
(2*S,4*S**,*Z*)-2-(5-azido-pent-3-enyl)-4-*tert*-butylcyclohexanone** (2-128b), **(2*S**,4*S**)-2-**

((S*)-3-azidopent-4-enyl)-4-tert-butylcyclohexanone (2-128c), and **(2S*,4S*)-2-((R*)-3-azidopent-4-enyl)-4-tert-butylcyclohexanone (2-128d)**. According to the procedure **II**, the mixture of (2S*,4S*,E)-2-(5-bromopent-3-enyl)-4-tert-butylcyclohexanone and (2S*,4S*,Z)-2-(5-bromopent-3-enyl)-4-tert-butylcyclohexanone (1.23 g, 4.10 mmol) afforded after chromatography (0.25-1.2% EtOAc/hexanes) a mixture of azides **2-128a**, **2-128b**, **2-128c**, and **2-128d** (0.90 g, 84%, 67:7:13:13 from ¹H NMR in acetone; 60:6:17:17 from ¹H NMR in CDCl₃) as a colorless oil. Azides **2-128a**, **2-128b**, **2-128c**, and **2-128d**: *R_f* = 0.45 (10% EtOAc/hexanes); IR (neat) 2953, 2093, 1711 cm⁻¹; HRMS (ESI) *m/z* calculated for (C₃₀H₅₀N₆O₂+Na)⁺ 549.3893 (corresponding to (2M+Na)⁺), found: 549.3894. Azide **2-128a**: ¹H NMR (400 MHz, acetone) δ 0.94 (s, 9H), 1.11-1.32 (m, 3H), 1.36-1.45 (m, 1H), 1.65-1.73 (m, 1H), 1.85-1.93 (m, 1H), 2.05-2.28 (m, 4H), 2.36-2.45 (m, 2H), 3.77 (d, *J* = 6.4 Hz, 2H), 5.54-5.62 (m, 1H), 5.77-5.86 (m, 1H); ¹³C NMR (100 MHz, acetone) δ 27.1 (3CH₃), 28.5 (CH₂), 28.8 (CH₂), 29.6 (CH₂), 32.1 (C), 34.9 (CH₂), 41.2 (CH₂), 46.9 (CH), 48.3 (CH), 52.3 (CH₂), 123.3 (CH), 136.6 (CH), 211.05 (C). Azide **2-128b** (diagnostic peaks only): ¹H NMR (400 MHz, acetone) δ 3.90 (d, *J* = 7.2 Hz, 2H); ¹³C NMR (100 MHz, acetone) δ 122.5 (CH), 135.8 (CH), 211.17 (C). Azides **2-128c** and **2-128d** (diagnostic peaks only): ¹H NMR (400 MHz, acetone) δ 3.96 (q, *J* = 7.2 Hz, 1H), 5.28-5.36 (m, 2H), 5.79-5.86 (m, 1H); ¹³C NMR (100 MHz, acetone) δ 48.8 (CH), 48.9 (CH), 65.1 (CH), 65.2 (CH), 117.4 (CH₂), 117.5 (CH₂), 136.2 (CH), 136.2 (CH), 210.97 (C), 211.00 (C).

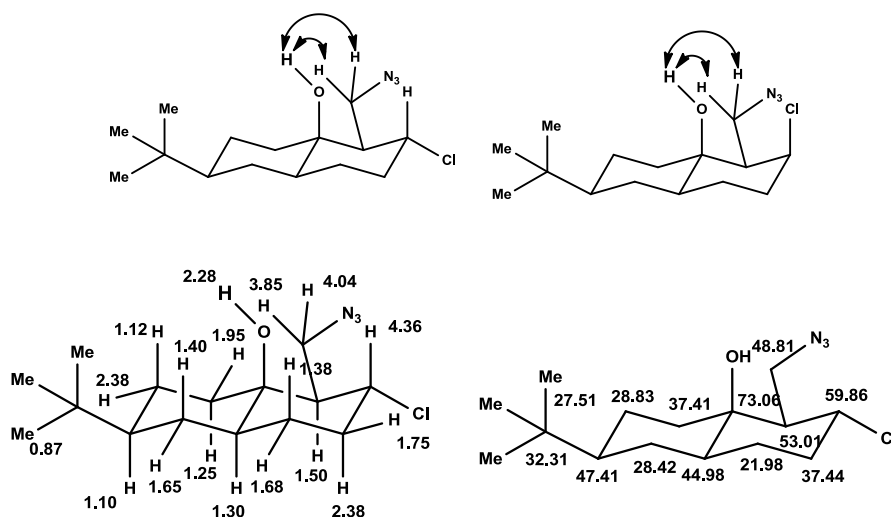


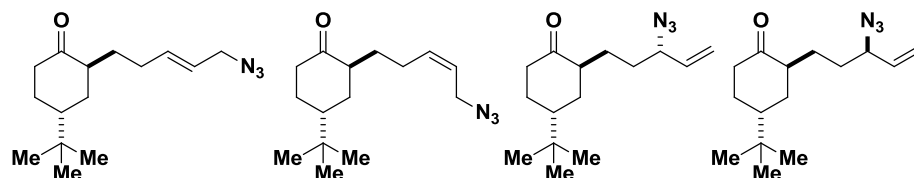
(**3R*,8S*,9aS***)-8-*tert*-Butyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-129a**) and (**3S*,8S*,9aS***)-8-*tert*-butyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-129b**). According to the procedure **VI**, azides **2-128a**, **2-128b**, **2-128c**, and **2-128d** (86 mg, 0.33 mmol) afforded after chromatography (10-100% EtOAc/hexanes) lactam **2-129a** (39 mg, 51%) as a colorless oil and lactam **2-129b** (13 mg, 17%) as a colorless oil. Lactam **2-129a**: R_f = 0.55 (100% EtOAc); IR (neat) 2951, 1637, 1416 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{15}\text{H}_{25}\text{NO}+\text{H})^+$ 236.2014, found: 236.2002; ^1H NMR (400 MHz, CDCl_3) δ 0.88 (s, 9H), 1.23-1.37 (m, 3H), 1.63-1.71 (m, 2H), 1.74-1.82 (m, 1H), 1.95-2.02 (m, 1H), 2.03-2.13 (m, 1H), 2.25-2.35 (m, 1H), 2.42-2.48 (m, 1H), 2.53-2.59 (m, 1H), 3.83 (t, J = 8.8 Hz, 1H), 4.70 (t, J = 6.0 Hz, 1H), 4.99-5.10 (m, 2H), 5.74-5.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.2 (CH_2), 27.7 (3 CH_3), 28.5 (CH_2), 32.5 (CH_2), 33.2 (C), 37.4 (CH_2), 37.7 (CH_2), 51.7 (CH), 58.6 (CH), 59.5 (CH), 113.7 (CH_2), 137.2 (CH), 173.6 (C). Lactam **2-129b**: R_f = 0.65 (100% EtOAc); IR (neat) 2960, 1637, 1416 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{15}\text{H}_{25}\text{NO}+\text{H})^+$ 236.2014, found: 236.2006; ^1H NMR (400 MHz, CDCl_3) δ 0.90 (s, 9H), 1.13-1.36 (m, 3H), 1.70-1.79 (m, 2H), 1.81-1.90 (m, 1H), 1.98-2.05 (m, 2H), 2.11-2.19 (m, 1H), 2.40 (dd, J = 12.0 Hz, 14.0 Hz, 1H), 2.64 (dd, J = 8.0 Hz, 14.0 Hz, 1H), 3.65-3.71 (m, 1H), 4.77 (t, J = 6.0 Hz, 1H), 5.10-5.17 (m, 2H), 5.78-5.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.3 (CH_2), 27.6 (3 CH_3), 29.1 (CH_2), 33.09 (CH_2), 33.11 (C), 37.2 (CH_2), 37.6 (CH_2), 51.5 (CH), 59.1 (CH), 59.7 (CH), 114.3 (CH_2), 137.9 (CH), 174.4 (C). The following data and NOE correlations were used to assign lactams **2-129a** and **2-129b**.



(2*S**,4*aR**,5*R**,6*R**,8*aS**)-5-(Azidomethyl)-2-(*tert*-butyl)-6-chlorodecahydro-naphthalen-4*a*-ol (2-129c) and (2*S**,4*aR**,5*R**,6*S**,8*aS**)-5-(azidomethyl)-2-(*tert*-butyl)-6-chlorodecahydronaphthalen-4*a*-ol (2-129d). According to the procedure VI, azides **2-128a**, **2-128b**, **2-128c**, and **2-128d** (79 mg, 0.30 mmol), titanium tetrachloride (0.48 mL, 1 M in dichloromethane, 0.48 mmol) and molecular sieves (1 g) at room temperature afforded after chromatography (3-100% EtOAc/hexanes) a mixture of lactams **2-129a** and **2-129b** (24 mg,

34%) and a mixture of alcohols **2-129c** and **2-129d** (2.5:1 ratio, 31 mg, 34%) as a colorless oil. Alcohol **2-129c** and **2-129d** (2.5:1 ratio): R_f = 0.60 (20% EtOAc/hexanes); IR (neat) 3533, 2940, 2101 cm^{-1} . Alchol **2-129c**: ^1H NMR (400 MHz, CDCl_3) δ 0.87 (s, 9H), 0.98-1.10 (m, 1H), 1.12 (q, J = 12.0 Hz, 1H), 1.21-1.32 (m, 2H), 1.33-1.45 (m, 3H), 1.49 (dt, J = 11.2, 3.0 Hz, 1H), 1.54-1.73 (m, 2H), 1.76 (qd, J = 13.4, 4.3 Hz, 1H), 1.96 (qt, J = 13.1, 3.2 Hz, 1H), 2.28 (d, J = 1.3 Hz, 1H), 2.37 (dq, J = 13.1, 3.2 Hz, 1H), 3.85 (dd, J = 13.0, 2.5 Hz, 1H), 4.04 (dd, J = 13.0, 3.3 Hz, 1H), 4.37 (td, J = 11.4, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.0 (CH_2), 27.51 (3CH_3), 28.4 (CH_2), 28.8 (CH_2), 32.31 (C), 37.41 (CH_2), 37.44 (CH_2), 45.0 (CH), 47.4 (CH), 48.8 (CH_2), 53.0 (CH), 59.9 (CH), 73.1 (C). Alcohol **2-129d** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 2.24 (q, J = 3.0 Hz, 1H), 2.51 (d, J = 2.5 Hz, 1H), 3.70 (dd, J = 12.5, 10.2 Hz, 1H), 3.80 (dd, J = 5.8, 10.4 Hz, 1H), 4.69 (q, J = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.9 (CH_2), 22.9 (CH_2), 27.49 (3CH_3), 29.0 (CH_2), 32.36 (C), 34.3 (CH_2), 36.6 (CH_2), 45.4 (CH), 47.7 (CH), 48.2(CH), 49.5 (CH_2), 61.9 (CH), 71.9 (C). The following data and NOE correlations were used to assign alcohols **2-129c** and **2-129d**.





(2*S**,4*R**,*E*)-2-(5-Azidopent-3-enyl)-4-*tert*-butylcyclohexanone (2-130a),

(2*S**,4*R**,*Z*)-2-(5-azido-pent-3-enyl)-4-*tert*-butylcyclohexanone (2-130b), (2*S**,4*R**)-2-

((*S**)-3-azidopent-4-enyl)-4-*tert*-butylcyclohexanone (2-130c), and (2*S**,4*R**)-2-((*R**)-3-

azidopent-4-enyl)-4-*tert*-butylcyclohexanone (2-130d). According to the general

procedure **III**, (2*S**,4*R**)-2-(but-3-enyl)-4-*tert*-butylcyclohexanone (63 mg, 0.30 mmol), HG-

2 (11 mg, 0.020 mmol), and allyl bromide (125 mg, 1.03 mmol) afforded a mixture of azides

2-130a, **2-130b**, **2-130c**, and **2-130d** (53 mg, 67%, 63:9:14:14 ratio from ¹H NMR in acetone)

as a colorless oil after column chromatography (0.3-1.6% EtOAc/hexanes). Azides **2-130a**, **2-**

130b, **2-130c**, and **2-130d**: *R*_f = 0.25 (10% EtOAc/hexanes); IR (neat) 2952, 2095, 1709 cm⁻¹;

HRMS (ESI) *m/z* calculated for (C₃₀H₅₀N₆O₂+Na)⁺ 549.3893 (corresponding to (2M+Na)⁺),

found: 549.3893. Azide **2-130a**: ¹H NMR (400 MHz, acetone) δ 0.94 (s, 9H), 1.46-1.62 (m,

2H), 1.66-1.75 (m, 2H), 1.80-1.90 (m, 2H), 1.95-2.13 (m, 3H), 2.15-2.25 (m, 1H), 2.36-2.50

(m, 2H), 3.78 (d, *J* = 6.4 Hz, 2H), 5.58-5.65 (m, 1H), 5.79-5.86 (m, 1H); ¹³C NMR (100 MHz,

acetone) δ 26.4 (CH₂), 26.8 (3CH₃), 29.6 (CH₂), 30.5 (CH₂), 31.1 (CH₂), 32.0 (C), 38.0 (CH₂),

41.2 (CH), 47.9 (CH), 52.3 (CH₂), 123.9 (CH), 135.7 (CH), 212.9 (C). Azide **2-130b**

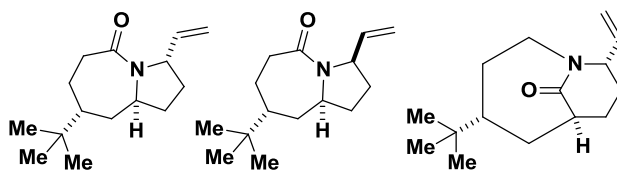
(diagnostic peaks only): ¹H NMR (400 MHz, acetone) δ 3.91 (d, *J* = 7.2 Hz, 2H); ¹³C NMR

(100 MHz, acetone) δ 122.9 (CH), 135.0 (CH), 212.97 (C). Azides **2-130c** and **2-130d**

(diagnostic peaks only): ¹H NMR (400 MHz, acetone) δ 3.97-4.04 (m, 1H), 5.28-5.36 (m,

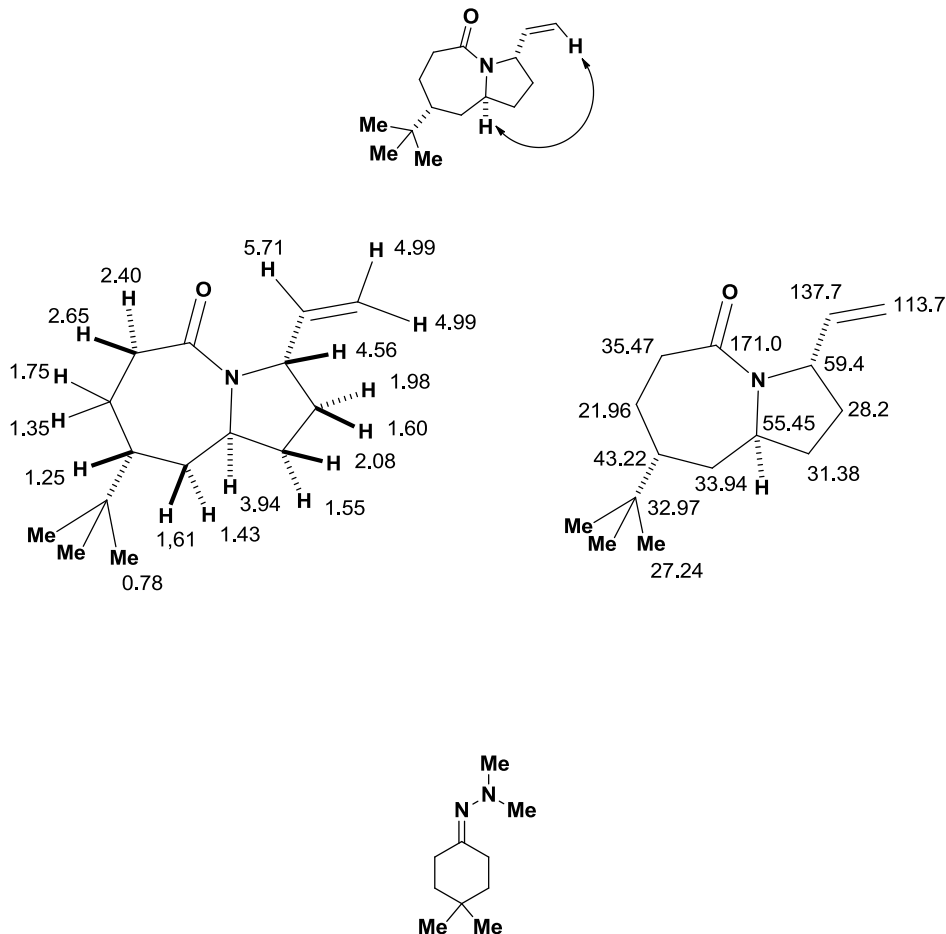
2H), 5.79-5.86 (m, 1H); ¹³C NMR (100 MHz, acetone) δ 48.26 (CH), 48.32 (CH), 64.54 (CH),

64.63 (CH), 117.7 (CH₂), 136.0 (CH), 212.87 (C), 212.90 (C).

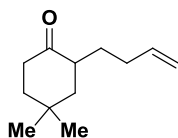


(3*S**,8*R**,9*aS**)-8-*tert*-Butyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2-131a), (3*R**,8*R**,9*aS**)-8-*tert*-butyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2-131b), and (4*S**,6*S**,9*S**)-4-*tert*-butyl-9-vinyl-1-azabicyclo[4.3.1]decan-10-one (2-131c). According to the procedure VI, the mixture of azides **2-130a**, **2-130b**, **2-130c**, and **2-130d** (48 mg, 0.18 mmol) afforded after chromatography (1/4-3/1 EtOAc/hexanes) lactam **2-131a** (24 mg, 56%) as a colorless oil and a mixture of lactams **2-131a**, **2-131b**, and **2-131c** (3 mg, 7%, 1:1:1 ratio) as a colorless oil. Lactam **2-131a**: R_f = 0.50 (100% EtOAc); IR (neat) 2950, 1632, 1408 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{15}\text{H}_{25}\text{NO}+\text{H})^+$ 236.2014, found: 236.1981; ^1H NMR (500 MHz, CDCl_3) δ 0.79 (s, 9H), 1.23-1.27 (m, 1H), 1.32-1.40 (m, 1H), 1.41-1.48 (m, 1H), 1.50-1.62 (m, 3H), 1.70-1.78 (m, 1H), 1.96-2.08 (m, 2H), 2.37-2.44 (m, 1H), 2.62-2.68 (m, 1H), 3.92-3.97 (m, 1H), 4.54-4.63 (m, 1H), 4.94-5.02 (m, 2H), 5.67-5.74 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.0 (CH_2), 27.2 (3 CH_3), 28.2 (CH_2), 31.4 (CH_2), 33.0 (C), 34.0 (CH_2), 35.5 (CH_2), 43.2 (CH), 55.5 (CH), 59.4 (CH), 113.7 (CH_2), 137.7 (CH), 171.0 (C). Lactams **2-131b** and **2-131c**: R_f = 0.45 (100% EtOAc); IR (neat): 2925, 1635, 1413 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{15}\text{H}_{25}\text{NO}+\text{Na})^+$ 258.1834, found: 258.1811; ^1H NMR (500 MHz, CDCl_3) (diagnostic peaks only) δ 0.80 (s, 9H), 0.82 (s, 9H), 3.55-3.63 (m, 1H), 3.85-3.91 (m, 1H), 4.54-4.63 (m, 1H), 4.67-4.73 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.5 (CH_2), 24.3 (CH_2), 27.2 (3 CH_3), 27.6 (3 CH_3), 29.1 (CH_2), 29.7 (CH_2), 32.4 (CH_2), 33.0 (C), 33.09 (CH_2), 33.12 (C), 34.3 (CH_2), 35.5 (CH_2), 37.2 (CH_2), 37.6 (CH_2), 43.5 (CH), 51.5 (CH), 55.9 (CH), 59.1 (CH), 59.7 (CH), 59.8 (CH), 114.3 (CH_2), 114.5 (CH_2),

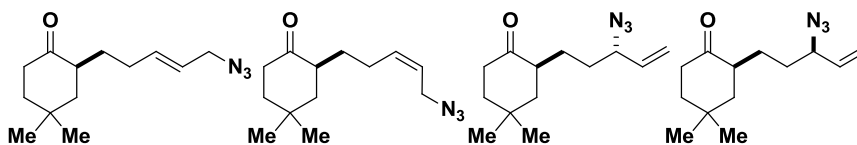
137.9 (CH), 138.4 (CH), 171.4 (C), 174.4 (C). The following data and NOE correlation were used to assign lactam **2-131a**.



2-(4,4-Dimethylcyclohexylidene)-1,1-dimethylhydrazine.¹⁰⁸ According to the general procedure **IV**, 4,4-dimethylcyclohexanone (2.0 g, 0.16 mmol) afforded 2-(4,4-dimethylcyclohexylidene)-1,1-dimethylhydrazine (2.7 g, 100%) as a colorless oil. IR (neat) 2951, 1636 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{21}\text{N}_2$ ($\text{M}+\text{H}$)⁺ 169.1705, found: 169.1709; ^1H NMR (400 MHz, CDCl_3) δ 1.00 (s, 6H), 1.43 (t, $J=6.4$ Hz, 2H), 1.49 (t, $J=6.4$ Hz, 2H), 2.26 (t, $J=6.4$ Hz, 2H), 2.43 (s, 6H), 2.52 (t, $J=6.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.6, 27.7, 30.3, 31.8, 38.8, 39.6, 47.5, 169.9.

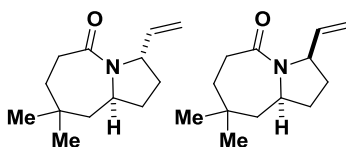


2-(But-3-enyl)-4,4-dimethylcyclohexanone.¹⁰⁹ According to the general procedure V, 2-(4,4-dimethylcyclohexylidene)-1,1-dimethylhydrazine (2.5 g, 15 mmol) afforded 2-(but-3-enyl)-4,4-dimethylcyclohexanone (1.75 g, 65%) as a colorless oil after chromatography (0.6-2% EtOAc/hexanes). R_f = 0.50 (10% EtOAc/hexanes); IR (neat) 2924, 1711 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{20}\text{ONa}$ ($\text{M}+\text{Na}$)⁺ 203.1412, found: 203.1457; ^1H NMR (400 MHz, CDCl_3) δ 1.02 (s, 3H), 1.14-1.23 (m, 1H), 1.21 (s, 3H), 1.32 (t, J = 13.2 Hz, 1H), 1.63 (dt, J = 4.6, 13.6 Hz, 1H), 1.70-1.82 (m, 2H), 1.88-1.98 (m, 1H), 2.03-2.10 (m, 2H), 2.25 (ddd, J = 2.8, 4.6, 14.0 Hz, 1H), 2.39-2.52 (m, 2H), 4.94-5.04 (m, 2H), 5.74-5.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.5 (CH_3), 28.0 (CH_2), 30.8 (C), 31.1 (CH_2), 31.5 (CH_3), 38.5 (CH_2), 40.1 (CH_2), 45.1 (CH), 46.7 (CH_2), 114.7 (CH_2), 138.5 (CH), 213.6 (C).



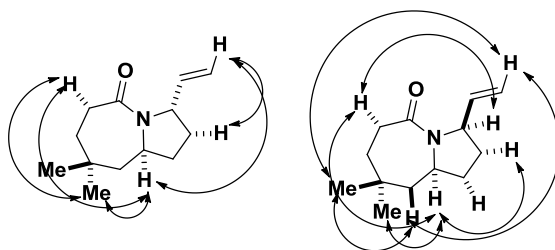
(*S,*E*)-2-(5-Azidopent-3-enyl)-4,4-dimethylcyclohexanone (2-122a), (*S**,*Z*)-2-(5-azido pent-3-enyl)-4,4-dimethylcyclohexanone (2-122b), (*S**)-2-((*S**)-3-azidopent-4-enyl)-4,4-dimethyl cyclohexanone (2-122c), and (*S**)-2-((*R**)-3-azidopent-4-enyl)-4,4-dimethylcyclohexanone (2-122d).** According to the general procedure III, 2-(but-3-enyl)-4,4-dimethylcyclohexanone (1.7 g, 9.4 mmol) and (HG-2, 2 mol%) afforded azides **2-122a**, **2-122b**, **2-122c**, and **2-122d** (1.43 g, 65%, 63:7:15:15 ratio from ^1H NMR in CDCl_3) as a colorless oil after chromatography (0.3-1.8% EtOAc/hexanes). Azides **2-122a**, **2-122b**, **2-122c**, and **2-122d**: R_f = 0.30 (10% EtOAc/hexanes); IR (neat) 2955, 2093, 1709, 1238 cm^{-1} ;

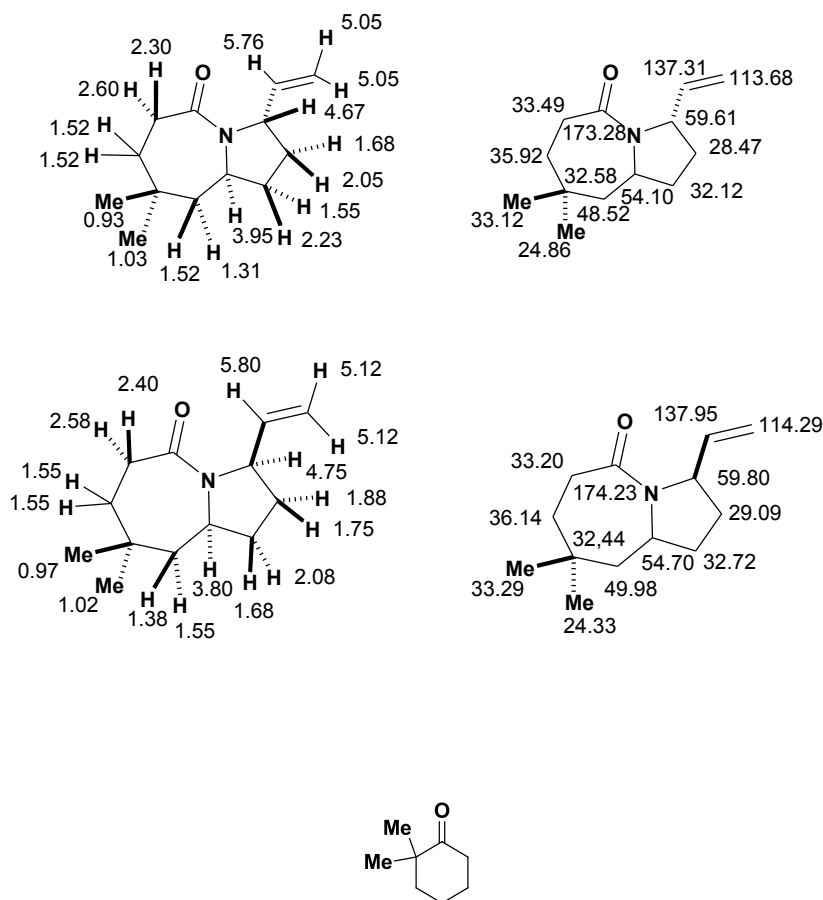
HRMS (ESI) m/z calculated for $C_{26}H_{43}N_6O_2$ ($2M+H$)⁺ 471.3447, found: 471.3436. Azide **2-122a**: ¹H NMR (400 MHz, CDCl₃) δ 1.01 (s, 3H), 1.16-1.38 (m, 3H), 1.21 (s, 3H), 1.56-1.68 (m, 1H), 1.70-1.80 (m, 2H), 1.88-1.96 (m, 1H), 2.11 (q, J = 7.2 Hz, 1H), 2.22-2.27 (m, 1H), 2.35-2.52 (m, 2H), 3.69 (d, J = 6.6 Hz, 2H), 5.49-5.56 (m, 1H), 5.69-5.77 (m, 1H); ¹H NMR (400 MHz, acetone) δ 1.02 (s, 3H), 1.10-1.38 (m, 2H), 1.26 (s, 3H), 1.53-1.65 (m, 1H), 1.71-1.86 (m, 3H), 2.03-2.15 (m, 3H), 2.45-2.55 (m, 2H), 3.70 (d, J = 4.8 Hz, 2H), 5.53-5.62 (m, 1H), 5.72-5.83 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.5 (CH₃), 28.3 (CH₂), 29.7 (CH₂), 30.8 (C), 31.4 (CH₃), 38.5 (CH₂), 40.1 (CH₂), 45.0 (CH), 46.8 (CH₂), 52.8 (CH₂), 123.2 (CH), 136.6 (CH), 213.35 (C); ¹³C NMR (100 MHz, acetone) δ 23.8 (CH₃), 28.6 (CH₂), 29.5 (CH₂), 30.6 (C), 30.9 (CH₃), 38.0 (CH₂), 39.8 (CH₂), 44.6 (CH), 46.5 (CH₂), 52.3 (CH₂), 123.3 (CH), 136.5 (CH), 211.3 (C). Azide **2-122b** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 3.79-3.82 (m, 2H); ¹H NMR (400 MHz, acetone) δ 3.89 (br, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 122.5 (CH), 135.72 (CH), 213.29 (C); ¹³C NMR (100 MHz, acetone) δ 122.5 (CH), 135.7 (CH). Azides **2-122c** and **2-122d** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 3.79-3.82 (m, 1H); 5.26-5.31 (m, 2H), 5.69-5.77 (m, 1H); ¹H NMR (400 MHz, acetone) δ 3.96 (q, J = 6.4 Hz, 1H), 5.27-5.36 (m, 2H), 5.76-5.86 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 65.21 (CH), 65.36 (CH), 118.11 (CH₂), 118.23 (CH₂), 135.60 (CH), 135.69 (CH), 212.96 (C), 213.04 (C); ¹³C NMR (100 MHz, acetone) δ 65.11 (CH), 65.14 (CH), 117.5 (CH₂), 136.15 (CH), 136.18 (CH).



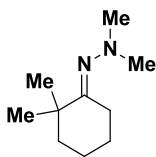
(**3S*,9aS***)-8,8-Dimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one
(**2-123a**) and (**3R*,9aS***)-8,8-dimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-

5(6*H*)-one (2-123b). According to general procedure VI, azides **2-122a**, **2-122b**, **2-122c**, and **2-122d** (215 mg, 0.915 mmol) afforded lactam **2-123a** (88 mg, 47%) as a colorless oil and lactam **2-123b** (52 mg, 28%) as a colorless oil after chromatography (5-15% EtOAc/hexanes). Lactam **2-123a**: R_f = 0.50 (100% EtOAc); IR (neat) 2951, 1632, 1416 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{21}\text{NONa}$ ($\text{M}+\text{Na}$) $^{+}$ 230.1521, found: 230.1521; ^1H NMR (400 MHz, CDCl_3) δ 0.93 (s, 3H), 1.03 (s, 3H), 1.31 (d, J = 14.0 Hz, 1H), 1.49-1.59 (m, 4H), 1.63-1.68 (m, 1H), 1.99-2.11 (m, 1H), 2.19-2.29 (m, 1H), 2.31-2.38 (m, 1H), 2.57-2.65 (m, 1H), 3.95 (t, J = 9.6 Hz, 1H), 4.68 (t, J = 7.0 Hz, 1H), 4.98-5.08 (m, 2H), 5.72-5.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.9 (CH_3), 28.5 (CH_2), 32.1 (CH_2), 32.6 (C), 33.1 (CH_3), 33.5 (CH_2), 35.9 (CH_2), 48.5 (CH_2), 54.1 (CH), 59.6 (CH), 113.7 (CH_2), 137.3 (CH), 173.3 (C). Lactam **2-123b**: R_f = 0.42 (100% EtOAc); IR (neat) 2954, 1635, 1414 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{22}\text{NO}$ ($\text{M}+\text{H}$) $^{+}$ 208.1701, found: 208.1704; ^1H NMR (400 MHz, CDCl_3) δ 0.97 (s, 3H), 1.02 (s, 3H), 1.38 (dd, J = 2.6, 14.2 Hz, 1H), 1.49-1.59 (m, 3H), 1.62-1.78 (m, 2H), 1.83-1.92 (m, 1H), 2.05-2.12 (m, 1H), 2.40 (ddd, J = 1.8, 7.2, 14.8 Hz, 1H), 2.54-2.61 (m, 1H), 3.77-3.84 (m, 1H), 4.75 (t, J = 6.0 Hz, 1H), 5.10-5.16 (m, 2H), 5.77-5.85 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.3 (CH_3), 29.1 (CH_2), 32.4 (C), 32.7 (CH_2), 33.2 (CH_2), 33.3 (CH_3), 36.2 (CH_2), 49.0 (CH_2), 54.7 (CH), 59.8 (CH), 114.3 (CH_2), 137.9 (CH), 174.2 (C). The following data and NOE correlations were used to assign lactams **2-123a** and **2-123b**.

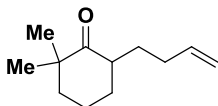




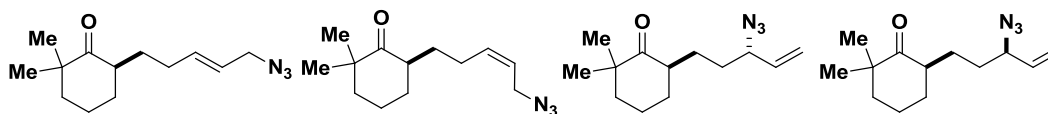
2,2-Dimethylcyclohexanone.¹¹⁰ To a mixture of sodium amide (50% w/w in toluene, 16.4 g, 0.21 mol) in THF (90 mL) was added dropwise 2-methylcyclohexanone (22.5 g, 0.20 mol) at room temperature under nitrogen atmosphere with the accompanying gas emission. The resulting mixture was refluxed for 2 h. After the mixture was cooled to 0 °C, methyl iodide (31.2 g, 0.22 mol) was added dropwise and the resulting mixture was refluxed for another 2 h. The reaction mixture was filtered, and the filtrate was washed with water, dried over anhydrous sodium sulfate and evaporated. The residue oil was distilled under reduced pressure (40 °C/15 mmHg) to afford the title ketone 2,2-dimethylcyclohexanone (11.5 g, 46%) as a colorless oil.



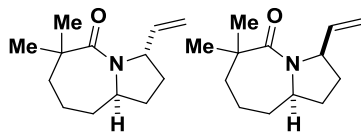
2-(2,2-Dimethylcyclohexylidene)-1,1-dimethylhydrazine. According to the general procedure **IV**, 2,2-dimethylcyclohexanone (5.8 g, 46 mmol), and 1,1-dimethylhydrazine (11.5 mL, 150 mmol) afforded 2-(2,2-dimethylcyclohexylidene)-1,1-dimethylhydrazine (6.80 g, 88%) as a colorless oil. IR (neat) 2929, 1709, 1449 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{21}\text{N}_2$ ($\text{M}+\text{H}$)⁺ 169.1705, found: 169.1737; ^1H NMR (400 MHz, CDCl_3) δ 1.10 (s, 6H), 1.48-1.53 (m, 2H), 1.58-1.62 (m, 2H), 2.39 (s, 6H), 2.40-2.43 (m, 2H), 2.52-2.55 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.8, 24.5, 26.9, 27.1, 41.3, 47.4, 47.6, 173.9.



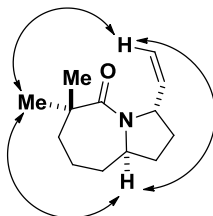
6-(But-3-enyl)-2,2-dimethylcyclohexanone. According to the general procedure **V**, 2-(2,2-dimethylcyclohexylidene)-1,1-dimethylhydrazine (6.80 g, 40 mmol) and 4-bromobutene (6.48 g, 48.0 mmol) afforded 6-(but-3-enyl)-2,2-dimethylcyclohexanone (1.10 g, 15%) as a colorless oil after column chromatography (0.5-1.2% EtOAc/hexanes). R_f = 0.60 (10% EtOAc/hexanes); IR (neat) 2929, 1703, 1452 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{21}\text{O}$ ($\text{M}+\text{H}$)⁺ 181.1592, found: 181.1628; ^1H NMR (400 MHz, CDCl_3) δ 1.05 (s, 3H), 1.18 (s, 3H), 1.19-1.23 (m, 1H), 1.30 (dq, J = 4.0, 13.2 Hz, 1H), 1.55 (dt, J = 4.0, 13.2 Hz, 1H), 1.65-1.72 (m, 1H), 1.75-1.82 (m, 1H), 1.83-1.95 (m, 2H), 2.03-2.10 (m, 3H), 2.56 (sextet, J = 6.4 Hz, 1H), 4.94-5.04 (m, 2H), 5.74-5.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.6 (CH_2), 25.1 (CH_3), 25.6 (CH_3), 28.5 (CH_2), 31.4 (CH_2), 34.6 (CH_2), 41.9 (CH_2), 45.1 (CH), 45.5 (C), 114.6 (CH_2), 138.7 (CH), 216.8 (C).

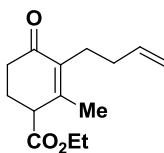


(*R,*E*)-6-(5-Azidopent-3-enyl)-2,2-dimethylcyclohexanone (2-126a), (*R**,*Z*)-6-(5-azido pent-3-enyl)-2,2-dimethylcyclohex-anone (2-126b), (*R**)-6-((*S**)-3-azidopent-4-enyl)-2,2-dimethyl cyclohexanone (2-126c), and (*R**)-6-((*R**)-3-azidopent-4-enyl)-2,2-dimethylcyclohexanone (2-126d).** According to the general procedure **III**, 6-(but-3-enyl)-2,2-dimethylcyclohexanone (1.10 g, 6.10 mmol), HG-2 (77 mg, 0.12 mmol) and allyl bromide (1.7 mL, 20 mmol) afforded a mixture of azides **2-126a**, **2-126b**, **2-126c**, and **2-126d** (0.63 g, 44%, 65:5:15:15 ratio from ^1H NMR in acetone) as a colorless oil after column chromatography (0.3-1% EtOAc/hexanes). Azides **2-126a**, **2-126b**, **2-126c**, and **2-126d**: R_f = 0.35 (10% EtOAc/hexanes); IR (neat) 2930, 2093, 1702 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{26}\text{H}_{43}\text{N}_6\text{O}_2$ ($2\text{M}+\text{H}$) $^+$ 471.3447, found: 471.3424. Azide **2-126a**: ^1H NMR (400 MHz, acetone) δ 0.99 (s, 3H), 1.18 (s, 3H), 1.18-1.35 (m, 2H), 1.53 (dt, J = 4.0, 13.2 Hz, 1H), 1.62-1.70 (m, 1H), 1.75-1.82 (m, 1H), 1.83-1.99 (m, 2H), 2.05-2.15 (m, 3H), 2.63-2.71 (m, 1H), 3.76 (d, J = 6.6 Hz, 2H), 5.53-5.61 (m, 1H), 5.76-5.86 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 21.3 (CH_2), 24.3 (CH_3), 25.2 (CH_3), 28.9 (CH_2), 29.7 (CH_2), 34.4 (CH_2), 41.6 (CH_2), 44.7 (CH), 45.0 (C), 52.3 (CH_2), 123.3 (CH), 136.6 (CH), 214.80 (C). Azide **2-126b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.90 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, acetone) δ 122.5 (CH), 135.8 (CH), 214.86 (C). Azides **2-126c** and **2-126d** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.96 (q, J = 6.8 Hz, 1H), 5.27-5.36 (m, 2H), 5.76-5.86 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 65.12 (CH), 65.18 (CH), 117.40 (CH_2), 117.44 (CH_2), 136.16 (CH), 136.22 (CH), 214.71 (C), 214.74 (C).



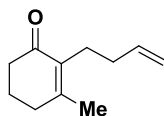
(3*S**,9*aR**)-6,6-Dimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-127a**) and (3*R**,9*aR**)-6,6-dimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-127b**). According to general procedure **VI**, azides **2-126a**, **2-126b**, **2-126c**, and **2-126d** (54 mg, 0.23 mmol) afforded a mixture of lactams **2-127a** and **2-127b** (24 mg, 50%, 10:1 ratio) as a colorless oil after chromatography (5-30% EtOAc/hexanes). Lactam **2-127a** and **2-127b**: R_f = 0.55 (50% EtOAc/hexanes); IR (neat) 2925, 1619, 1398 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{22}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 208.1701, found: 208.1700. Lactam **2-127a**: ^1H NMR (400 MHz, CDCl_3) δ 1.23 (s, 3H), 1.28 (s, 3H), 1.48-1.67 (m, 4H), 1.70-1.83 (m, 4H), 1.90-2.00 (m, 1H), 2.18-2.28 (m, 1H), 3.97-4.02 (m, 1H), 4.75-4.78 (m, 1H), 5.01-5.08 (m, 2H), 5.70-5.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.9 (CH_2), 24.3 (CH_3), 27.8 (CH_2), 29.5 (CH_3), 32.4 (CH_2), 35.5 (CH_2), 37.0 (CH_2), 42.5 (C), 57.4 (CH), 61.6 (CH), 113.2 (CH_2), 138.1 (CH), 177.1 (C). Lactam **2-127b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.24 (s, 3H), 1.27 (s, 3H), 3.80-3.86 (m, 1H), 5.00-5.13 (m, 2H), 5.75-5.80 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.4 (CH_2), 30.6 (CH_3), 33.2 (CH_2), 35.9 (CH_2), 37.7 (CH_2), 42.2 (C), 58.6 (CH), 61.9 (CH), 113.9 (CH_2), 138.5 (CH), 176.9 (C). The following NOE correlations were used to assign lactam **2-127a**.





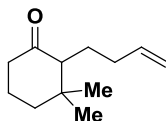
Ethyl 3-(but-3-en-1-yl)-2-methyl-4-oxocyclohex-2-enecarboxylate (2-80).¹¹¹

Hagemann's ester (90% purity, 20.4 g, 0.100 mol) was rapidly added to a stirred solution of potassium *tert*-butoxide (12.1 g, 0.110 mol) in dry *tert*-butanol (60 mL). The red solution so formed turned into a straw-yellow suspension a few minutes after the addition. The mixture was stirred for 15 min before 4-bromo-1-butene (14.6 g, 0.110 mol) was added in a single portion. The mixture was allowed to reflux overnight. The mixture was allowed to cool to room temperature then was partitioned between 0.5 M aqueous HCl and dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate and concentrated to afford ester **2-80** (24.5 g, 104%), which was used without further purification. Ester **2-80**: ¹H NMR (400 MHz, CDCl₃) δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.96-2.10 (m, 2H), 1.99 (s, 3H), 2.15-2.30 (m, 2H), 2.32-2.42 (m, 3H), 2.52-2.65 (m, 1H), 3.29 (t, *J* = 4.8 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.91-5.02 (m, 2H), 5.76-5.86 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.2 (CH), 20.5 (CH), 24.9 (CH₂), 25.6 (CH₂), 32.9 (CH₂), 34.7 (CH₂), 47.7 (CH), 61.2 (CH₂), 114.7 (CH₂), 136.9 (C), 138.2 (CH), 150.3 (C), 172.2 (C), 197.4 (C).



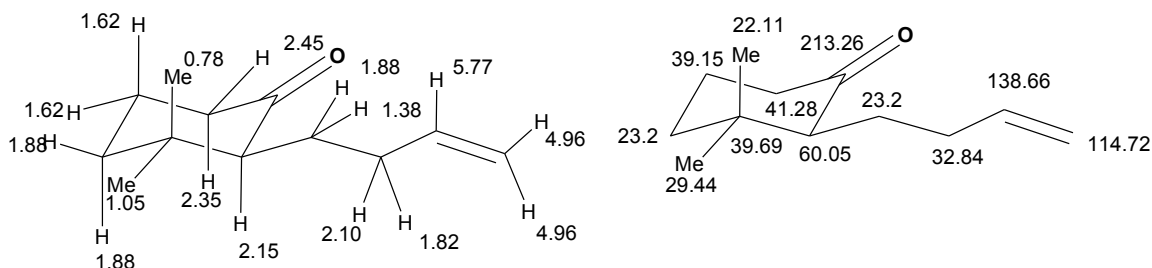
2-(But-3-enyl)-3-methylcyclohex-2-enone (2-81).¹¹¹ Ester **2-80** (8.1g, 34 mmol) was dissolved in a 1/1 mixture of ethanol and water (40 mL) and LiOH·H₂O (2.86 g, 68.0 mmol) was added as a powder. The mixture was stirred overnight, concentrated, and the residue partitioned between water and diethyl ether. The aqueous phase was acidified with 6 M

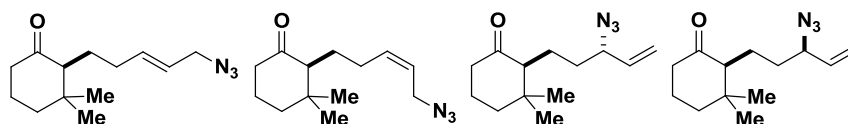
aqueous HCl and extracted with dichloromethane. The organic extracts were dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in a mixture of concentrated HCl (3 mL) in THF (50 mL) and heated for 24 h at 90 °C. The mixture was concentrated. The residue was partitioned between water and dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed (2.5-5% EtOAc/hexanes) to yield ketone **2-81** as a dark-yellow oil (3.08 g, 50% two steps). Ketone **2-81**: R_f = 0.40 (20% EtOAc/hexanes); IR (neat) 2927, 1660, 1379 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{11}\text{H}_{16}\text{O}+\text{H})^+$ 165.1279, found: 165.1270; ^1H NMR (400 MHz, CDCl_3) δ 1.94 (s, 3H), 1.90-1.96 (m, 2H), 2.04-2.10 (m, 2H), 2.33-2.41 (m, 6H), 4.91-5.02 (m, 2H), 5.77-5.87 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.3 (CH_3), 22.3 (CH_2), 24.7 (CH_2), 32.9 (CH_2), 33.2 (CH_2), 37.9 (CH_2), 114.5 (CH_2), 135.0 (C), 138.5 (CH), 155.6 (C), 198.7 (C).



2-(But-3-enyl)-3,3-dimethylcyclohexanone (2-82).¹¹¹ Lithium chloride (158 mg, 37.5 mmol, flame-dried) and copper(I) iodide were dissolved in anhydrous THF (120 mL) under argon at rt. The resulting solution was cooled to -40 °C using a dry ice/acetonitrile bath, ketone **2-81** (3.08 g, 18.8 mmol) and chlorotrimethylsilane (2.24 g, 20.6 mmol) were added, and the solution stirred for 10 min. MeMgCl (3 M in THF, 9.4 mL, 28.1 mmol) was added dropwise and left stirring at -40 °C for 1.5 h. The reaction mixture was then poured into 150 mL of saturated aqueous ammonium chloride and 150 mL of diethyl ether, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (2-(but-

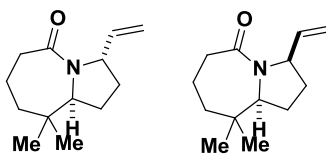
3-enyl)-3,3-dimethylcyclohex-1-enyloxy)trimethylsilane (4.42 g), which was used without further purification. IR (neat) 2934, 1252, 1196 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{15}\text{H}_{28}\text{OSi}+\text{H})^+$ 253.1988, found: 253.1913; ^1H NMR (400 MHz, CDCl_3) δ 0.20 (s, 9H), 1.02 (s, 6H), 1.39-1.42 (m, 2H), 1.63-1.69 (m, 2H), 1.99-2.06 (m, 4H), 2.14-2.20 (m, 2H), 4.92-5.06 (m, 2H), 5.83-5.93 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.8 (CH_2), 19.4 (CH_2), 26.2 (CH_2), 28.5 (2CH_3), 30.8 (CH_2), 33.9 (CH_2), 34.5 (C), 39.2 (CH_2), 113.5 (CH_2), 123.1 (C), 139.9 (CH), 144.3 (C). The silyl enol ether was dissolved in THF (40 mL) and stirred with TBAF (1 M in THF, 28.1 mL, 28.1 mmol) at rt for 30 min under N_2 atmosphere. The mixture was poured into water and diethyl ether, and the aqueous layer extracted with diethyl ether. The combined organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated to yield a residue, which was purified by chromatography (1.5% EtOAc/hexanes) to afford ketone **2-82** (2.60 g, 77% for two steps). Ketone **2-82**: R_f = 0.30 (5% EtOAc/hexanes); IR (neat) 2962, 1708 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{24}\text{H}_{40}\text{O}_2+\text{Na})^+$ 383.2926 (corresponding to $(2\text{M}+\text{Na})^+$), found: 383.2923; ^1H NMR (400 MHz, CDCl_3) δ 0.78 (s, 3H), 1.05 (s, 3H), 1.34-1.42 (m, 1H), 1.58-1.69 (m, 2H), 1.77-1.94 (m, 4H), 2.06-2.15 (m, 2H), 2.23-2.38 (m, 2H), 4.94-5.01 (m, 2H), 5.72-5.83 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.1 (CH_3), 23.2 (CH_2), 29.4 (CH_3), 32.8 (CH_2), 39.2 (CH_2), 39.7 (C), 41.3 (CH_2), 60.1 (CH), 114.7 (CH_2), 138.7 (CH), 213.3 (C). The following data were used to assign ketone **2-82**.





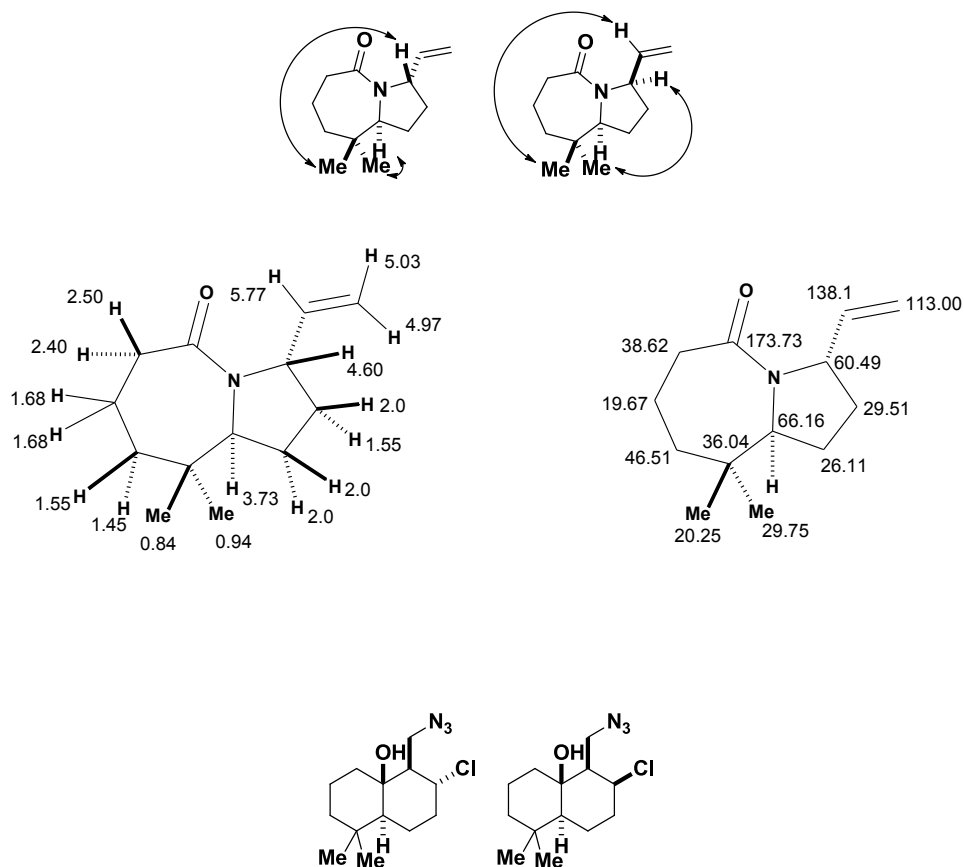
(*S**,*E*)-2-(5-Azidopent-3-enyl)-3,3-dimethylcyclohexanone (**2-120a**), (*S**,*Z*)-2-(5-azido pent-3-enyl)-3,3-dimethylcyclohexanone (**2-120b**), (*R**)-2-((*S**)-3-azidopent-4-enyl)-3,3-dimethyl cyclo-hexanone (**2-120c**), and (*R**)-2-((*R**)-3-azidopent-4-enyl)-3,3-dimethylcyclo hexanone (**2-120d**). According to the general procedure **III**, ketone **2-82** (1.6 g, 8.9 mmol), HG-2 (179 mg, 0.450 mmol) and allyl bromide (3.8 mL, 45 mmol) afforded a mixture of azides **2-120a**, **2-120b**, **2-120c**, and **2-120d** (1.60 g, 77%, 67:9:12:12 ratio from ¹H NMR in CDCl₃) as a colorless oil after column chromatography (0.6-4.0% EtOAc/hexanes). Azides **2-120a**, **2-120b**, **2-120c**, and **2-120d**: *R*_f = 0.15 (5% EtOAc/hexanes); IR (neat) 2954, 2094, 1706 cm⁻¹; HRMS (ESI) *m/z* calculated for (C₂₆H₄₂N₆O₂+H)⁺ 471.3447 (corresponding to (2M+H)⁺), found: 471.3417. Azide **2-120a**: ¹H NMR (500 MHz, CDCl₃) δ 0.76 (s, 3H), 1.04 (s, 3H), 1.22-1.38 (m, 1H), 1.55-1.68 (m, 2H), 1.76-1.93 (m, 4H), 2.07-2.18 (m, 2H), 2.23-2.35 (m, 2H), 3.67-3.72 (m, 2H), 5.46-5.54 (m, 1H), 5.68-5.76 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 21.9 (CH₃), 23.16 (CH₂), 23.18 (CH₂), 29.5 (CH₃), 31.3 (CH₂), 39.3 (CH₂), 39.8 (C), 41.4 (CH₂), 52.8 (CH₂), 59.8 (CH), 123.3 (CH), 136.7 (CH), 213.09 (C); ¹H NMR (500 MHz, acetone) δ 0.76 (s, 3H), 1.06 (s, 3H), 1.28-1.43 (m, 1H), 1.55-1.62 (m, 1H), 1.69-1.95 (m, 5H), 2.08-2.18 (m, 1H), 2.21-2.28 (m, 2H), 2.29-2.39 (m, 1H), 3.76 (m, 2H), 5.54-5.58 (m, 1H), 5.79-5.86 (m, 1H); ¹³C NMR (125 MHz, acetone) δ 26.3 (CH₃), 28.1 (CH₂), 28.2 (CH₂), 34.2 (CH₃), 36.4 (CH₂), 44.4 (CH₂), 44.5 (C), 46.2 (CH₂), 57.6 (CH₂), 64.5 (CH), 128.6 (CH), 141.7 (CH), 216.2 (C). Azide **2-120b** (diagnostic peaks only): ¹H NMR (500 MHz, CDCl₃) δ 0.767 (s, 3H), 1.055 (s, 3H), 3.65-3.75 (m, 2H); ¹³C NMR (125 MHz, CDCl₃)

δ 122.7 (CH), 135.7 (CH), 213.07 (C); ^1H NMR (500 MHz, acetone) δ 3.83-3.88 (m, 2H); ^{13}C NMR (125 MHz, acetone) δ 64.7 (CH), 127.8 (CH), 140.9 (CH). Azides **2-120c** and **2-120d** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 0.753 (s, 3H), 1.04 (s, 3H), 3.77-3.84 (m, 1H); 5.25-5.29 (m, 2H), 5.68-5.76 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 64.8 (CH), 65.4 (CH), 118.1 (CH_2), 118.2 (CH_2), 135.6 (CH), 135.7 (CH), 212.91 (C), 212.94 (C); ^1H NMR (500 MHz, acetone) δ 3.92-4.00 (m, 1H), 5.25-5.38 (m, 2H), 5.79-5.86 (m, 1H); ^{13}C NMR (125 MHz, acetone) δ 67.0 (CH), 70.4 (CH), 122.6 (CH_2), 122.8 (CH_2), 141.3 (CH), 141.4 (CH).



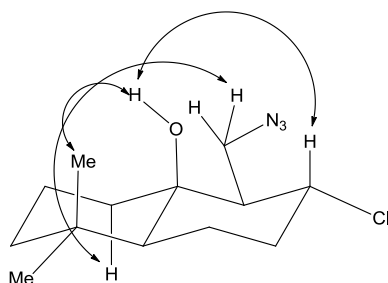
(**3S*,9aR***)-9,9-Dimethyl-3-vinyl-hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (**2-121a**) and (**3S*,9aR***)-9,9-dimethyl-3-vinyl-hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (**2-121b**). According to the procedure **VI**, azides **2-120a**, **2-120b**, **2-120c**, and **2-120d** (130 mg, 0.550 mmol) and tin tetrachloride (1 M in chloromethane, 0.83 mL, 0.83 mmol) afforded a mixture of lactams **2-121a** and **2-121b** (65 mg, 57%, 30:1 ratio) as a colorless oil after chromatography (15-25% EtOAc/hexanes). Lactams **2-121a** and **2-121b**: R_f = 0.35 (100% EtOAc/hexanes); IR (neat) 2966, 2927, 1634, 1408 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{13}\text{H}_{21}\text{NO}+\text{Na})^+$ 230.1521, found: 230.1449. Lactam **2-121a**: ^1H NMR (400 MHz, CDCl_3) δ 0.84 (s, 3H), 0.94 (s, 3H), 1.42-1.70 (m, 5H), 1.91-2.08 (m, 3H), 2.35-2.42 (m, 1H), 2.48-2.53 (m, 1H), 3.73 (dd, J = 2.4, 8.0 Hz, 1H), 4.60 (t, J = 5.2 Hz, 1H), 4.94-5.05 (m, 2H), 5.72-5.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.7 (CH_2), 20.3 (CH_3), 26.1 (CH_2), 29.5 (CH_2), 29.8 (CH_3), 36.0 (C), 38.6 (CH_2), 46.5 (CH_2), 60.5 (CH), 66.2 (CH), 113.0 (CH_2), 138.1 (CH), 173.7 (C). Lactam **2-121b** (diagnostic peaks only): ^1H NMR (400 MHz,

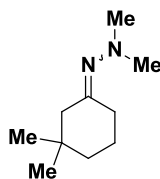
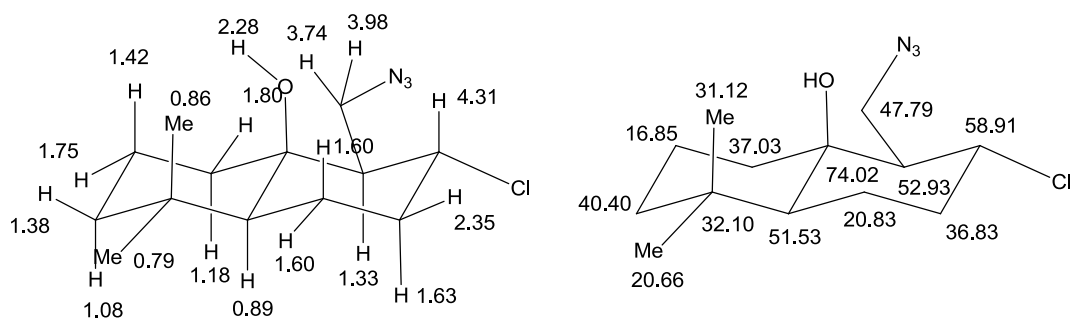
CDCl₃) δ 0.79 (s, 3H), 0.87 (s, 3H), 3.58 (dd, J = 6.4 Hz, 9.6 Hz, 1H), 4.79 (t, J = 6.2 Hz, 1H), 5.05-5.21 (m, 2H), 5.72-5.82 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 19.0 (CH₃), 19.5 (CH₂), 27.9 (CH₂), 28.0 (CH₂), 28.7 (CH₃), 34.6 (C), 38.2 (CH₂), 46.0 (CH₂), 60.0 (CH), 66.9 (CH), 115.0 (CH₂), 138.1 (CH), 174.5 (C). The following data and NOE correlations were used to assign lactams **2-121a** and **2-121b**.



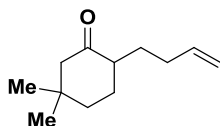
(**4aR***,**5R***,**6R***,**8aS***)-5-(Azidomethyl)-6-chloro-1,1-dimethyldecahydro-naphthalen-4a-ol (**2-121c**) and (**4aR***,**5R***,**6S***,**8aS***)-5-(azidomethyl)-6-chloro-1,1-dimethyldecahydronaphthalen-4a-ol (**2-121d**). According to the procedure **VI**, azides **2-120a**, **2-120b**, **2-120c**, and **2-120d** (92 mg, 0.39 mmol) and titanium tetrachloride (1 M in chloromethane, 0.60 mL, 0.60 mmol) afforded a mixture of lactams **2-121a** and **2-112b** (20

mg, 25%, 1:1.1 ratio) as a colorless oil and a mixture of alcohols **2-121c** and **2-121d** (8 mg, 8%, 4:1 ratio) after chromatography (1-25% EtOAc/hexanes) as a colorless oil. Alcohols **2-121c** and **2-121d**: $R_f = 0.70$ (20% EtOAc/hexanes). Alcohol **2-121c**: ^1H NMR (500 MHz, CDCl_3) δ 0.79 (s, 3H), 0.86 (s, 3H), 0.86-0.96 (m, 1H), 1.09 (qd, $J = 13.4, 3.3$ Hz, 1H), 1.17 (dd, $J = 14.0, 3.1$ Hz, 1H), 1.30-1.44 (m, 3H), 1.56-1.67 (m, 3H), 1.75 (dt, $J = 13.5, 3.4$ Hz, 1H), 1.78-1.82 (m, 1H), 2.28 (d, $J = 1.7$ Hz, 1H), 2.31-2.41 (m, 1H), 3.75 (dd, $J = 13.0, 2.6$ Hz, 1H), 3.98 (dd, $J = 13.0, 2.9$ Hz, 1H), 4.31 (td, $J = 11.2, 4.8$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 16.9 (CH_2), 20.7 (CH_3), 20.8 (CH_2), 31.1 (CH_3), 32.1 (C), 36.8 (CH_2), 37.0 (CH_2), 40.4 (CH_2), 47.8 (CH_2), 51.5 (CH), 52.9 (CH), 58.9 (CH), 74.0 (C). Alcohol **2-121d** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 0.82 (s, 3H), 0.92 (s, 3H), 1.86 (dq, $J = 11.5, 1.5$ Hz, 1H), 2.24 (dq, $J = 14.3, 2.9$ Hz, 1H), 2.49 (d, $J = 2.7$ Hz, 1H), 3.56 (dd, $J = 12.4, 10.1$ Hz, 1H), 3.70 (dd, $J = 12.4, 4.8$ Hz, 1H), 4.59 (q, $J = 2.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 14.9 (CH_2), 16.6 (CH_2), 20.5 (CH_3), 31.2 (CH_3), 32.3 (C), 33.9 (CH_2), 36.1 (CH_2), 40.5 (CH_2), 48.2 (CH), 48.4 (CH_2), 51.7 (CH), 60.8 (CH), 72.7 (C). The following data and NOE correlations were used to assign alcohol **2-121c**.



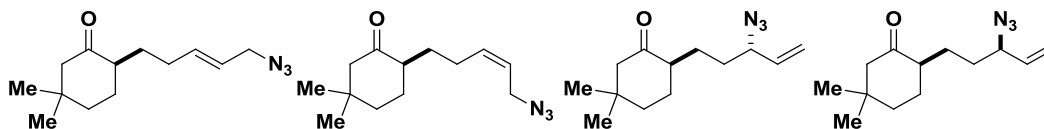


2-(3,3-Dimethylcyclohexylidene)-1,1-dimethylhydrazine. According to the general procedure IV, 3,3-dimethylcyclohexanone (10.0 g, 79.2 mmol) and 1,1-dimethylhydrazine (18.3 mL, 240 mmol) afforded 2-(3,3-dimethylcyclohexylidene)-1,1-dimethylhydrazine (12.3 g, 92%, 1:1 ratio) as a colorless oil, which was used directly in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 0.93 (s, 3H), 0.94 (s, 3H), 1.42-1.47 (m, 2H), 1.63-1.75 (m, 2H), 2.03 (s, 1H), 2.19 (t, *J* = 6.4 Hz, 1H), 2.35 (s, 1H), 2.40 (s, 3H), 2.45 (s, 3H), 2.45 (t, *J* = 6.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 22.1 (CH₂), 22.8 (CH₂), 27.8 (CH₂), 28.2 (CH₃), 28.6 (CH₃), 33.2 (C), 34.2 (C), 35.2 (CH₂), 39.0 (CH₂), 39.2 (CH₂), 41.2 (CH₂), 47.4 (CH₃), 47.7 (CH₃), 48.6 (CH₂), 169.4 (C), 170.3 (C).



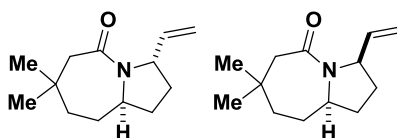
2-(But-3-enyl)-5,5-dimethylcyclohexanone. According to the general procedure V, 2-(3,3-dimethylcyclohexylidene)-1,1-dimethylhydrazine (5.05 g, 30.0 mmol) afforded 2-(but-

3-enyl)-5,5-dimethylcyclohexanone (3.91 g, 72%) as a colorless oil after chromatography (0.5-2.5% EtOAc/hexanes). R_f = 0.50 (10% EtOAc/hexanes); IR (neat) 2954, 1710 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{12}\text{H}_{20}\text{O}+\text{H})^+$ 181.1592, found: 181.1606; ^1H NMR (400 MHz, CDCl_3) δ 0.88 (s, 3H), 1.05 (s, 3H), 1.24-1.33 (m, 1H), 1.45-1.55 (m, 1H), 1.56-1.70 (m, 2H), 1.86-1.95 (m, 1H), 1.98-2.15 (m, 4H), 2.18-2.27 (m, 2H), 4.94-5.04 (m, 2H), 5.74-5.84 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.7 (CH_3), 28.3 (CH_2), 29.4 (CH_2), 31.2 (CH_2), 31.3 (CH_3), 37.0 (C), 38.0 (CH_2), 48.7 (CH), 54.9 (CH_2), 114.7 (CH_2), 138.5 (CH), 212.8 (C).



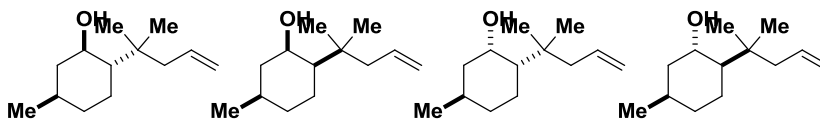
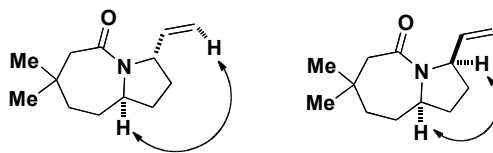
(*S,*E*)-2-(5-Azidopent-3-enyl)-5,5-dimethylcyclohexanone (2-124a)**, **(*S**,*Z*)-2-(5-azidopent-3-enyl)-5,5-dimethylcyclohexanone (2-124b)**, **(*R**)-2-((*S**)-3-azidopent-4-enyl)-5,5-dimethylcyclohexanone (2-124c)**, and **(*R**)-2-((*R**)-3-azidopent-4-enyl)-5,5-dimethylcyclohexanone (2-124d)**. According to the general procedure **III**, 2-(but-3-enyl)-5,5-dimethylcyclohexanone (1.28 g, 7.10 mmol), HG-2 (89 mg, 0.14 mmol) and allyl boromide (1.80 mL, 21.3 mmol) afforded a mixture of azides **2-124a**, **2-124b**, **2-124c**, and **2-124d** (872 mg, 52%, 63:7:15:15 ratio) as colorless oil after column chromatography (0.1-1.6% EtOAc/hexanes). Azides **2-124a**, **2-124b**, **2-124c**, and **2-124d**: R_f = 0.30 (10% EtOAc/hexanes); IR (neat) 2952, 2093, 1708, 1236 cm^{-1} ; HRMS (ESI) m/z calculated $(\text{C}_{26}\text{H}_{42}\text{N}_6\text{O}_2+\text{H})^+$ 471.3447 (corresponding to $(2\text{M}+\text{H})^+$), found: 471.3432. Azide **2-124a**: ^1H NMR (400 MHz, acetone) δ 0.85 (s, 3H), 1.05 (s, 3H), 1.22-1.31 (m, 1H), 1.42-1.62 (m, 3H), 1.69-1.79 (m, 1H), 1.81-1.92 (m, 1H), 1.99-2.08 (m, 2H), 2.09-2.19 (m, 1H), 2.28-2.36 (m, 2H), 3.77 (d, J = 6.4 Hz, 2H), 5.55-5.62 (m, 1H), 5.77-5.86 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 24.9 (CH_2), 28.6 (CH_3), 29.3 (CH_2), 29.6 (CH_2), 30.8 (CH_3), 36.4 (C), 37.7 (CH_2),

48.1 (CH), 52.3 (CH₂), 54.5 (CH₂), 123.3 (CH), 136.5 (CH), 210.65 (C). Azide **2-124b** (diagnostic peaks only): ¹H NMR (400 MHz, acetone) δ 3.90 (d, *J* = 7.2 Hz, 2H); ¹³C NMR (100 MHz, acetone) δ 122.6 (CH), 135.7 (CH), 210.75 (C). Azides **2-124c** and **2-124d** (diagnostic peaks only): ¹H NMR (400 MHz, acetone) δ 3.97 (q, *J* = 7.0 Hz, 1H); 5.28-5.36 (m, 2H), 5.77-5.86 (m, 1H); ¹³C NMR (100 MHz, acetone) δ 48.55 (CH₂), 48.62 (CH₂), 65.0 (CH), 65.1 (CH), 117.52 (CH₂), 117.54 (CH₂), 136.12 (CH), 136.16 (CH), 210.58 (C).



(**3S*,9aR***)-7,7-Dimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-125a**) and (**3S*,9aR***)-7,7-dimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-125b**). According to the general procedure **VI**, azides **2-124a**, **2-124b**, **2-124c**, and **2-124d** (125 mg, 0.530 mmol) afforded lactam **2-125a** (53 mg, 48%) as a colorless oil and lactam **2-125b** (7 mg, 6%) as a colorless oil after column chromatography (10-50% EtOAc/hexanes). Lactam **2-125a**: *R_f* = 0.60 (100% EtOAc); IR (neat) 2956, 1631, 1414 cm⁻¹; HRMS (ESI) *m/z* calculated for (C₁₃H₂₁NO+H)⁺ 208.1701, found: 208.1701; ¹H NMR (400 MHz, CDCl₃) δ 1.00 (s, 6H), 1.53-1.70 (m, 5H), 1.71-1.82 (m, 1H), 1.98-2.10 (m, 1H), 2.20-2.31 (m, 1H), 2.24 (d, *J* = 13.2 Hz, 1H), 2.62 (d, *J* = 13.2 Hz, 1H), 3.81 (t, *J* = 9.6 Hz, 1H), 4.71 (t, *J* = 6.0 Hz, 1H), 4.99-5.08 (m, 2H), 5.71-5.80 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 23.7 (CH₃), 28.5 (CH₂), 30.3 (C), 31.8 (CH₂), 32.3 (CH₂), 33.6 (CH₃), 43.6 (CH₂), 50.7 (CH₂), 59.0 (CH), 59.5 (CH), 113.8 (CH₂), 137.3 (CH), 171.3 (C). Lactam **2-125b**: *R_f* = 0.52 (100% EtOAc); IR (neat) 2956, 2925, 1635, 1415 cm⁻¹; HRMS (ESI) *m/z* calculated for (C₁₃H₂₁NO+H)⁺ 208.1701, found: 208.1712; ¹H NMR (500 MHz, CDCl₃) δ 0.93 (s, 3H), 0.97 (s, 3H), 1.41 (dt, *J* = 4.0 Hz, 13.5 Hz, 1H), 1.51-1.28 (m, 2H), 1.65-1.80 (m, 4H), 2.01-2.07

(m, 1H), 2.22 (dd, $J = 2.0$ Hz, 13.5 Hz, 1H), 2.46 (d, $J = 13.5$ Hz, 1H), 3.55 (dd, $J = 9.0$ Hz, 16.0 Hz, 1H), 4.65 (t, $J = 6.0$ Hz, 1H), 5.02-5.16 (m, 2H), 5.72-5.80 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.6 (CH_3), 27.9 (CH_2), 29.5 (C), 31.43 (CH_2), 31.47 (CH_2), 32.8 (CH_3), 42.2 (CH_2), 49.5 (CH_2), 58.4 (CH), 59.0 (CH), 113.5 (CH_2), 137.0 (CH), 170.9 (C). The following NOE correlations were used to assign lactams **2-125a** and **2-125b**.

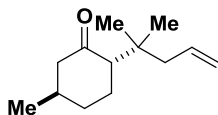


(1*R*,2*S*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol, (1*S*,2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol, (1*R*,2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol and (1*S*,2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol.

A solution of (*R*)-(+)-pulegone (85% purity, 12.5 g, 70.0 mmol) in dichloromethane (150 mL) was stirred at -78 °C as titanium tetrachloride (neat, 8.4 mL, 77 mmol) was added dropwise over 5 min to form a red solution. After stirring 10 min, a solution of allyltrimethylsilane (10.4 g, 91.0 mmol) in dichloromethane (30 mL) was added dropwise over 5 min. The resulting purple solution was stirred at -78 °C for 10 min and at 0 °C for an additional 10 min. A solution of triethylamine (70 mL) and methanol (22 mL) was added dropwise over 5 min, forming a white heterogeneous mixture that was diluted with diethyl ether (300 mL) and filtered. The mixture was washed with 10% HCl, saturated aqueous sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give

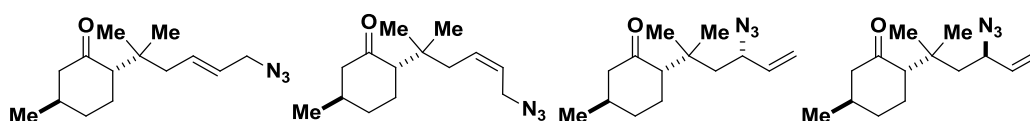
a crude product, which was purified by chromatography (0.6-5% EtOAc/hexanes) to afford a mixture of (2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone and (2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone (15.3 g, 96%, 1.3:1 ratio) as a colorless oil. To a solution of (2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone and (2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone (11.5 g, 59.0 mmol) in methanol (110 mL) at 0 °C was added portionwise sodium borohydride (3.37 g, 88.7 mmol). After being allowed to stir overnight, water was added slowly to quench the reaction. Diethyl ether was used to extract the product, and the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography (0.6-5% EtOAc/hexanes) to afford a mixture of (1*R*,2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol and (1*S*,2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol (2.50 g, 22%, 2:5 ratio) as a colorless oil, a mixture of alcohols (1*R*,2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol, (1*S*,2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol, (1*R*,2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol and (1*S*,2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol (3.80 g, 33%) as a colorless oil, and a mixture of (1*R*,2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol and (1*S*,2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol (3.68 g, 32%, 25:1 ratio) as a colorless oil. (1*R*,2*S*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol and (1*S*,2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol (2:5 ratio): R_f = 0.25 (10% EtOAc/hexanes); IR (neat) 3424, 2916, 1638, 1455 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{24}\text{ONa}$ ($\text{M}+\text{Na}$)⁺ 219.1725, found: 219.1772; (1*S*,2*S*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol: ¹H NMR (400 MHz, CDCl_3) δ 0.89 (d, J = 6.2 Hz, 3H), 0.95 (s, 3H), 0.98 (s, 3H), 0.88-1.02 (m, 1H), 1.07-1.20 (m, 2H), 1.47-1.60 (m, 2H), 1.71-1.82 (m, 3H), 2.03-2.15 (m, 2H), 4.25 (br, 1H), 5.00-

5.06 (m, 2H), 5.80-5.90 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9 (CH_2), 22.3 (CH_3), 25.4 (CH_3), 25.98 (CH_3), 26.2 (CH), 35.4 (C), 35.6 (CH_2), 44.0 (CH_2), 45.8 (CH_2), 48.6 (CH), 68.3 (CH), 116.8 (CH_2), 136.0 (CH). (1*R*,2*S*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 0.91 (d, J = 6.4 Hz, 3H), 0.97 (s, 3H), 1.03 (s, 3H), 1.37-1.45 (m, 1H), 1.63-1.68 (m, 1H), 1.89-1.96 (m, 1H), 2.15-2.30 (m, 2H), 3.58 (dt, J = 4.0, 10.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.0 (CH_3), 26.04 (CH_2), 26.4 (CH_3), 26.6 (CH_3), 31.7 (CH), 34.9 (CH_2), 35.7 (CH_2), 46.7 (CH_2), 46.9 (CH_2), 50.9 (CH), 73.1 (CH), 116.5 (CH_2), 136.5 (CH). (1*R*,2*R*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol and (1*S*,2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol (25:1 ratio): R_f = 0.30 (10% EtOAc/hexanes); IR (neat) 3506, 2910, 1638 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{24}\text{ONa}$ ($\text{M}+\text{Na}$) $^+$ 219.1725, found: 219.1728; (1*R*,2*R*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol: ^1H NMR (400 MHz, CDCl_3) δ 0.96 (s, 3H), 0.98 (s, 3H), 1.08-1.18 (m, 2H), 1.19 (d, J = 7.4 Hz, 3H), 1.27-1.33 (m, 1H), 1.37-1.44 (m, 1H), 1.51-1.60 (m, 1H), 1.62-1.77 (m, 2H), 1.89-1.97 (m, 1H), 2.03-2.17 (m, 2H), 4.26 (br, 1H), 5.00-5.06 (m, 2H), 5.80-5.90 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 15.9 (CH_2), 21.3 (CH or CH_3), 25.2 (CH or CH_3), 25.9 (CH or CH_3), 26.5 (CH or CH_3), 32.6 (CH_2), 35.6 (C), 40.7 (CH_2), 45.7 (CH_2), 49.1 (CH), 69.2 (CH), 116.7 (CH_2), 136.1 (CH). (1*S*,2*R*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.00 (s, 3H), 3.83 (br, 1H).



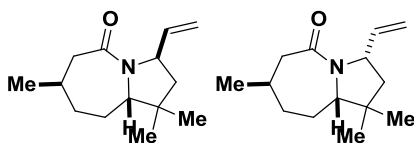
(2*S*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone. To a solution of (1*R*,2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol and (1*S*,2*S*,5*R*)-5-methyl-2-(2-

methylpent-4-en-2-yl)cyclohexanol (2.50 g, 12.7 mmol) in dichloromethane (40 mL) at room temperature was added silica gel (7.50 g) and pyridinium chlorochromate (PCC, 5.50 g, 25.5 mmol) slowly. After being allowed to stir overnight, the reaction mixture was concentrated, purified by chromatography (0.6-3% EtOAc/hexanes) to afford ketone (2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone (2.20 g, 88%) as a colorless oil. Its spectral data matched reported data.¹⁰²



(2*S*,5*R*,*E*)-2-(6-Azido-2-methylhex-4-en-2-yl)-5-methylcyclohexanone (**2-166a**), (2*S*,5*R*,*Z*)-2-(6-azido-2-methylhex-4-en-2-yl)-5-methylcyclohexanone (**2-166b**), (2*S*,5*R*)-2-((*S*)-4-azido-2-methylhex-5-en-2-yl)-5-methylcyclohexanone (**2-166c**), and (2*S*,5*R*)-2-((*R*)-4-azido-2-methylhex-5-en-2-yl)-5-methylcyclohexanone (**2-166d**). According to the general procedure **III**, (2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone (1.55 g, 8.0 mmol), HG-2 (250 mg, 0.400 mmol) and allyl bromide (2.0 mL, 24 mmol) afforded a mixture of azides **2-166a**, **2-166b**, **2-166c**, and **2-166d** (1.41 g, 71%, 89:9:1:1 from ¹³C NMR in CDCl₃, 90:8:1:1 from ¹³C NMR in acetone) as a colorless oil after column chromatography (0.6-4.0% EtOAc/hexanes). Azides **2-166a**, **2-166b**, **2-166c**, and **2-166d**: *R*_f = 0.35 (5% EtOAc/hexanes); IR (neat) 2954, 2094, 1708 cm⁻¹; HRMS (ESI) *m/z* calculated for C₂₈H₄₇N₄O₂ (2M-N₂+H)⁺ 471.3699, found: 471.3673. Azide **2-166a**: ¹H NMR (500 MHz, CDCl₃) δ 0.89 (s, 3H), 0.93 (dd, *J* = 1.0, 6.2 Hz, 3H), 0.95 (s, 3H), 1.22-1.32 (m, 1H), 1.35-1.45 (m, 1H), 1.76-1.86 (m, 2H), 1.94 (t, *J* = 12.5 Hz, 1H), 1.96-2.04 (m, 2H), 2.11 (dd, *J* = 4.7, 13.0 Hz, 1H), 2.18 (td, *J* = 2.0, 10.0 Hz, 1H), 2.33 (dd, *J* = 8.5, 13.5 Hz, 1H), 3.63 (d, *J* = 6.5 Hz, 2H), 5.40-5.47 (m, 1H), 5.62-5.68 (m, 1H); ¹H NMR (500 MHz, acetone) δ 0.91 (s,

3H), 0.93 (d, J = 6.5 Hz, 3H), 0.97 (s, 3H), 1.28-1.43 (m, 2H), 1.73-1.81 (m, 1H), 1.82-1.87 (m, 1H), 1.96-2.04 (m, 1H), 2.05-2.12 (m, 3H), 2.18 (ddd, J = 1.0, 4.5, 13.0 Hz, 1H), 2.33 (dd, J = 7.5, 13.5 Hz, 1H), 3.72 (d, J = 6.7 Hz, 2H), 5.46-5.52 (m, 1H), 5.76-5.80 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.3 (CH_3), 24.2 (CH_3), 25.4 (CH_3), 28.2 (CH_2), 34.5 (C), 34.62 (CH_2), 36.4 (CH), 43.1 (CH_2), 52.4 (CH_2), 52.9 (CH_2), 56.7 (CH), 125.4 (CH), 133.6 (CH), 212.1 (C); ^{13}C NMR (125 MHz, acetone) δ 22.6 (CH_3), 24.5 (CH_3), 25.5 (CH_3), 28.8 (CH_2), 35.1 (C), 35.3 (CH_2), 37.1 (CH), 43.8 (CH_2), 52.7 (CH_2), 53.3 (CH_2), 57.1 (CH), 126.6 (CH_2), 134.3 (CH), 211.6 (C). Azide **2-166b** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 2.43 (dd, J = 8.7, 14.0 Hz, 1H), 3.70-3.78 (m, 2H); ^1H NMR (500 MHz, acetone) δ 2.43 (dd, J = 8.7, 14.0 Hz, 1H), 3.81-3.87 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 124.4 (CH), 132.1 (CH), 211.98 (C); ^{13}C NMR (125 MHz, acetone) δ 125.3 (CH), 132.9 (CH), 211.8 (C). Azides **2-166c** and **2-166d** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 3.70-3.78 (m, 1H); ^1H NMR (500 MHz, acetone) δ 3.85-3.88 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 61.97 (CH), 62.03 (CH), 117.1 (CH_2), 117.2, (CH_2) 136.7 (CH), 136.9 (CH); ^{13}C NMR (125 MHz, acetone) δ 62.60 (CH), 62.74 (CH), 117.42 (CH_2), 117.57 (CH_2), 138.14 (CH), 138.21 (CH).



(**3R,7R,9aS**)-1,1,7-Trimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-167a**) and (**3S,7R,9aS**)-1,1,7-trimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (**2-167b**). According to the general procedure **VI**, azides **2-166a**, **2-166b**, **2-166c**, and **2-166d** (63 mg, 0.25 mmol) and tin tetrachloride (0.38 mL, 1 M in dichloromethane, 0.38 mmol) afforded lactam **2-167a** (17 mg, 30%) as a colorless oil and 2-

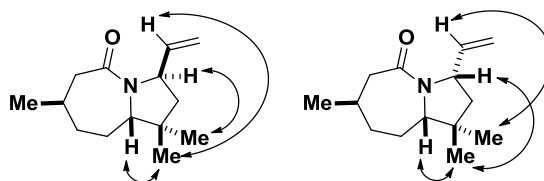
167b (11 mg, 20%) as a colorless oil after column chromatography (10-18% EtOAc/hexanes).

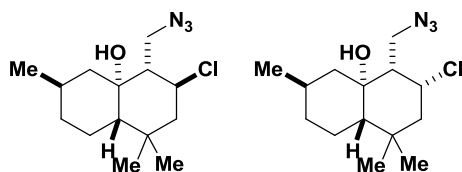
Lactam **2-167a**: $R_f = 0.5$ (100% EtOAc/hexanes); $[\alpha]_{546}^{25} -48.0$ (c 3.75, dichloromethane); IR

(neat) 2954, 1638, 1408 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{23}\text{NONa}$ ($\text{M}+\text{Na}$) $^{+}$ 244.1677, found: 244.1708; ^1H NMR (500 MHz, CDCl_3) δ 0.93 (s, 3H), 0.96 (d, $J = 6.5$ Hz, 3H), 1.07 (s, 3H), 1.13-1.27 (m, 2H), 1.54 (dd, $J = 6.0, 12.5$ Hz, 1H), 1.68-1.75 (m, 1H), 1.77-1.82 (m, 1H), 1.87 (dd, $J = 8.0, 12.5$ Hz, 1H), 1.90-1.95 (m, 1H), 2.27-2.37 (m, 2H), 3.31 (d, $J = 10.0$ Hz, 1H), 4.45 (dd, $J = 6.5, 14.0$ Hz, 1H), 5.03 (td, $J = 1.0, 9.0$ Hz, 1H), 5.08 (td, $J = 1.0, 17.0$ Hz, 1H), 5.79-5.86 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 23.7 (CH_3), 24.2 (CH_3), 28.5 (CH_3), 29.9 (CH), 30.1 (CH_2), 38.5 (CH_2), 41.2 (C), 45.0 (CH_2), 46.8 (CH_2), 59.6 (CH), 69.0 (CH), 113.7 (CH_2), 140.5 (CH), 173.4 (C). Lactam **2-167b**: $R_f = 0.4$ (100%

EtOAc/hexanes); $[\alpha]_{546}^{25} -25.6$ (c 2.35, dichloromethane); IR (neat) 2954, 1638, 1406 cm^{-1} ;

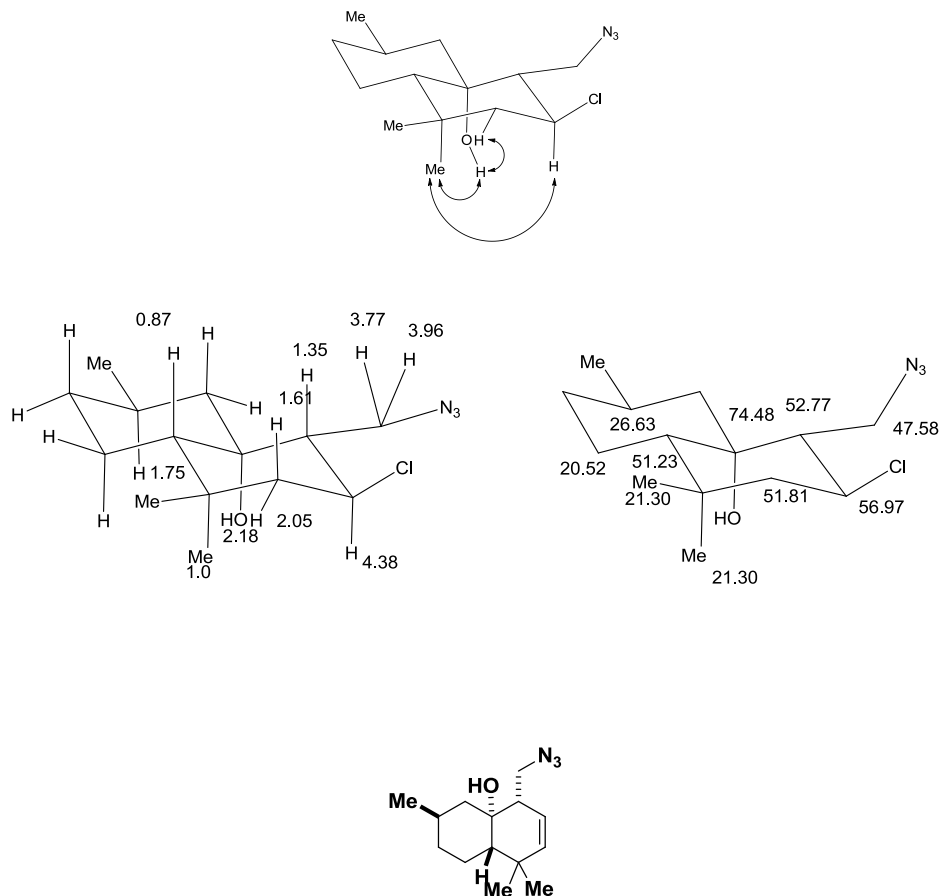
HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{23}\text{NONa}$ ($\text{M}+\text{Na}$) $^{+}$ 244.1677, found: 244.1676; ^1H NMR (500 MHz, CDCl_3) δ 0.92 (d, $J = 6.5$ Hz, 3H), 0.94 (s, 3H), 1.03 (s, 3H), 1.13-1.32 (m, 2H), 1.55 (dd, $J = 6.5, 12.5$ Hz, 1H), 1.68-1.75 (m, 1H), 1.77-1.82 (m, 2H), 1.88-1.94 (m, 1H), 2.26-2.35 (m, 2H), 3.22 (d, $J = 10.5$ Hz, 1H), 4.39-4.45 (m, 1H), 5.00 (td, $J = 1.3, 10.0$ Hz, 1H), 5.06 (td, $J = 1.3, 17.0$ Hz, 1H), 5.73-5.81 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 24.0 (CH_3), 24.6 (CH_3), 29.0 (CH_3), 30.23 (CH_2), 30.26 (CH), 39.0 (CH_2), 41.3 (C), 44.4 (CH_2), 46.6 (CH_2), 59.0 (CH), 69.2 (CH), 113.8 (CH_2), 140.0 (CH), 174.0 (C). The following NOE correlations were used to assign lactams **2-167a** and **2-167b**.





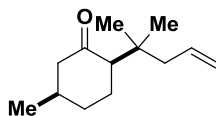
(3*S*^{*},4*S*^{*},4*aS*^{*},6*R*^{*},8*aS*^{*})-4-(Azidomethyl)-3-chloro-1,1,6-trimethyldecahydro-naphthalen-4a-ol (**2-167c**) and (3*R*^{*},4*S*^{*},4*aS*^{*},6*R*^{*},8*aS*^{*})-4-(azidomethyl)-3-chloro-1,1,6-trimethyldecahydronaphthalen-4a-ol (**2-167d**). According to the general procedure **VI**, azides **2-166a**, **2-166b**, **2-166c**, and **2-166d** (19 mg, 0.076 mmol) and titanium tetrachloride (1 M in dichloromethane, 0.12 mL, 0.12 mmol) at room temperature afforded a mixture of alcohols **2-167c** and **2-167d** (20:1 ratio, 14 mg, 64%) as a colorless oil after column chromatography (0.5-1% EtOAc/hexanes). Alcohol **2-167c**: R_f = 0.70 (20% EtOAc/hexanes); IR (neat) 3531, 2948, 2103, 1456 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{14}\text{H}_{24}\text{ClN}_3\text{O}$ (M)⁺ 285.1608, found: 285.1613; ^1H NMR (500 MHz, CDCl_3) δ 0.75-0.87 (m, 3H), 0.83 (d, J = 7.5 Hz, 3H), 0.84 (s, 3H), 0.95 (s, 3H), 1.35-1.43 (m, 2H), 1.47-1.53 (m, 1H), 1.61 (t, J = 12.5 Hz, 1H), 1.67-1.77 (m, 3H), 2.05 (dd, J = 4.0, 13.0 Hz, 1H), 2.19 (d, J = 1.1 Hz, 1H), 3.77 (dd, J = 2.5, 13.0 Hz, 1H), 3.96 (dd, J = 3.5, 13.0 Hz, 1H), 4.38 (dt, J = 3.8, 12.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 20.5 (CH_2), 21.30 (CH_3), 21.31 (CH_3), 26.6 (CH), 30.9 (CH_3), 33.8 (CH_2), 34.4(C), 46.3 (CH_2), 47.6 (CH_2), 51.2 (CH), 51.8 (CH_2), 52.8 (CH), 57.0 (CH), 74.5 (C). Alcohol **2-167d** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 2.12 (dd, J = 2.7, 15.3 Hz, 1H), 2.33 (d, J = 2.0 Hz, 1H), 3.67 (dd, J = 10.2, 12.5 Hz, 1H), 3.80 (dd, J = 4.7, 12.5 Hz, 1H), 4.60 (q, J = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 20.6 (CH_2), 23.0 (CH or CH_3), 26.2 (CH or CH_3), 31.5(C), 32.7 (CH or CH_3), 34.2 (CH_2), 45.8 (CH_2), 45.9 (CH_2),

47.2 (CH), 48.5 (CH₂), 51.3 (CH), 58.7 (CH), 72.4 (C). The following data and NOE correlations were used to assign alcohol **2-167c**.

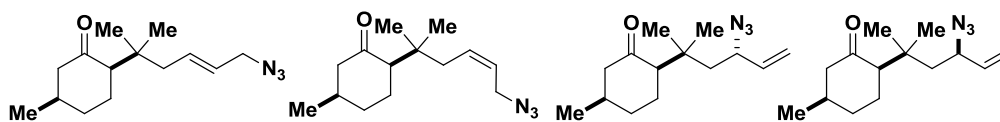


(3*R,4*aS**,5*S**,8*aS**)-5-(Azidomethyl)-3,8,8-trimethyl-1,2,3,4,4*a*,5,8,8*a*-octahydronaphthalen-4*a*-ol (**2-167c**). According to the general procedure **VI**, azides **2-166a**, **2-166b**, **2-166c**, and **2-166d** (69 mg, 0.28 mmol) and titanium tetrachloride (1 M in dichloromethane, 0.42 mL, 0.42 mmol) at room temperature afforded a mixture of alcohol **2-167c**, **2-167d** and **2-167e** (22:1:2 ratio, 26 mg, 33%) as a colorless oil, and a mixture of lactams **2-167a** and **2-167b** (20 mg, 33%, 1:1.7 ratio) after column chromatography (0.5-40% EtOAc/hexanes). Alcohol **2-167e** (diagnostic peaks only): ¹H NMR (500 MHz, CDCl₃) δ 3.24 (dd, *J* = 12.3, 8.4 Hz, 1H), 3.63 (dd, *J* = 12.3, 4.6 Hz, 1H), 5.36 (dd, *J* = 10.2, 1.7 Hz, 1H),**

5.54 (dd, $J = 10.2, 2.8$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.4 (CH or CH_3), 22.6 (CH_2), 24.7 (CH or CH_3), 28.0 (CH or CH_3), 30.6 (CH or CH_3), 34.9 (CH_2), 45.6 (CH), 46.0 (CH_2), 48.9 (CH), 51.7 (CH_2), 71.9 (C), 121.6 (CH), 140.2 (CH).

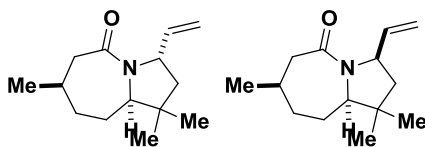


(2*R*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone. To a solution of (1*R*,2*R*,5*R*)-5-Methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol and (1*S*,2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanol (3.68 g, 18.8 mmol) in dichloromethane (40 mL) at room temperature was added silica gel (10 g) and pyridinium chlorochromate (PCC, 8.08 g, 37.5 mmol) slowly. After stirring overnight, the reaction mixture was concentrated, purified by chromatography (0.6-3% EtOAc/hexanes) to afford (2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone (2.23 g, 61%) as a colorless oil. Its spectral data matched reported data.¹⁰²



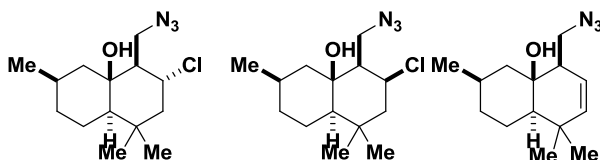
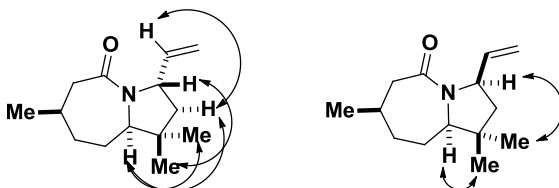
(2*R*,5*R*,*E*)-2-(6-Azido-2-methylhex-4-en-2-yl)-5-methylcyclohexanone (2-164a), (2*R*,5*R*,*Z*)-2-(6-azido-2-methylhex-4-en-2-yl)-5-methylcyclohexanone (2-164b), (2*R*,5*R*)-2-((*S*)-4-azido-2-methylhex-5-en-2-yl)-5-methylcyclohexanone (2-164c), and (2*R*,5*R*)-2-((*R*)-4-azido-2-methylhex-5-en-2-yl)-5-methylcyclohexanone (2-164d). According to the general procedure **III**, (2*R*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone (2.23 g, 11.5 mmol). HG-2 (360 mg, 0.570 mmol) and allyl bromide (2.0 mL, 24 mmol) afforded a mixture of azides **2-164a**, **2-164b**, **2-164c**, and **2-164d** (1.97 g, 69%, 94:5:0.5:0.5 ratio from

^{13}C NMR in CDCl_3 , 94:5:0.5:0.5 from ^{13}C NMR in acetone) as a colorless oil after column chromatography (0.6-4.0% EtOAc/hexanes). Azides **2-164a**, **2-164b**, **2-164c**, and **2-164d**: R_f = 0.5 (5% EtOAc/hexanes); IR (neat) 2957, 2094, 1707 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{28}\text{H}_{47}\text{N}_6\text{O}_2(2\text{M}+\text{H})^+$ 499.3760, found: 499.3738. Azide **2-164a**: ^1H NMR (500 MHz, CDCl_3) δ 0.95 (d, J = 7.0 Hz, 3H), 0.98 (s, 3H), 1.03 (s, 3H), 1.58-1.65 (m, 1H), 1.76 (dq, J = 3.5, 12.0 Hz, 1H), 1.82-1.90 (m, 1H), 1.93-1.98 (m, 1H), 2.03-2.12 (m, 2H), 2.22 (dd, J = 5.5, 11.5 Hz, 1H), 2.33-2.39 (m, 2H), 2.50 (dd, J = 5.5, 12.8 Hz, 1H), 3.71 (d, J = 6.6 Hz, 2H), 5.49-5.57 (m, 1H), 5.72-5.78 (m, 1H); ^1H NMR (500 MHz, acetone) δ 0.91 (d, J = 7.1 Hz, 3H), 0.97 (s, 3H), 1.02 (s, 3H), 1.58-1.45 (m, 1H), 1.67-1.78 (m, 1H), 1.88-1.97 (m, 3H), 2.10 (dd, J = 7.5, 13.5 Hz, 1H), 2.28-2.38 (m, 3H), 2.55 (dd, J = 6.8, 12.5 Hz, 1H), 3.76 (d, J = 6.6 Hz, 2H), 5.51-5.57 (m, 1H), 5.70-5.86 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 19.1 (CH or CH_3), 24.0 (CH_2), 24.5 (CH or CH_3), 25.4 (CH or CH_3), 31.4 (CH_2), 32.3 (CH or CH_3), 34.9 (C), 43.3 (CH_2), 50.3 (CH_2), 52.9 (CH_2), 57.0 (CH), 125.5 (CH), 133.6 (CH), 212.8 (CH_2); ^{13}C NMR (125 MHz, acetone) δ 19.1 (CH or CH_3), 24.6 (CH_2), 24.72 (CH or CH_3), 25.5 (CH or CH_3), 32.0 (CH_2), 33.0 (CH or CH_3), 35.4 (C), 43.9 (CH_2), 50.8 (CH_2), 53.3 (CH_2), 57.5 (CH), 126.6 (CH), 134.2 (CH), 212.06 (C). Azide **2-164b** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 3.79-3.84 (m, 2H); ^1H NMR (500 MHz, acetone) δ 2.45 (dd, J = 8.7, 14.0 Hz, 1H), 3.83-3.91 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 57.2 (CH), 124.5 (CH_2), 132.0 (CH_2), 212.7 (CH_2); ^{13}C NMR (125 MHz, acetone) δ 57.7 (CH), 125.3 (CH), 132.8 (CH), 212.28 (C). Azides **2-164c** and **2-164d** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 3.79-3.84 (m, 1H); ^1H NMR (500 MHz, acetone) δ 3.83-3.91 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 62.02 (CH), 62.05 (CH), 117.13 (CH_2), 117.19 (CH_2), 136.77 (CH), 136.91 (CH), 212.12 (C), 212.42 (C); ^{13}C NMR (125 MHz, acetone) δ 62.63 (CH), 62.73 (CH), 117.43 (CH_2), 117.53 (CH_2), 138.16 (CH), 138.22 (CH), 211.8 (C), 212.14 (C).



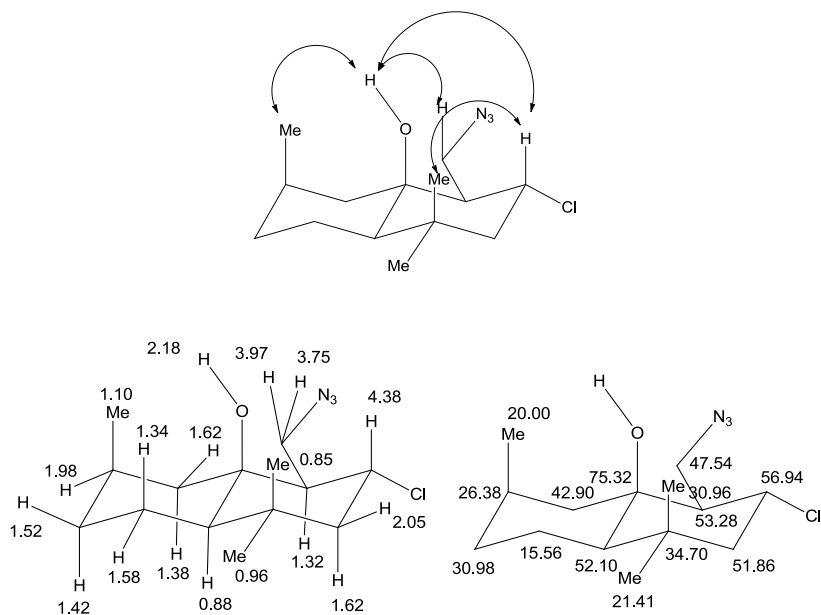
(3*S*,7*R*,9*aR*)-1,1,7-Trimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2-165a) and **(3*R*,7*R*,9*aR*)-1,1,7-trimethyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2-165b)**. According to the general procedure **VI**, azides **2-164a**, **2-164b**, **2-164c**, and **2-164d** (50 mg, 0.20 mmol) afforded lactam **2-165a** (19 mg, 43%) as a colorless oil and **2-165b** (2 mg, 5%) as a colorless oil after column chromatography (11-25% EtOAc/hexanes). Lactam **2-165a**: R_f = 0.5 (100% EtOAc/hexanes); $[\alpha]_{546}^{25} +12.7$ (c 0.75, dichloromethane); IR (neat) 2955, 1629, 1410 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{23}\text{NONa}$ ($\text{M}+\text{Na}$) $^{+}$ 244.1677, found: 244.1632; ^1H NMR (500 MHz, CDCl_3) δ 0.78 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.98 (s, 3H), 1.31-1.37 (m, 2H), 1.41 (dd, J = 9.8, 12.5 Hz, 1H), 1.48-1.55 (m, 1H), 1.65-1.73 (m, 2H), 1.85 (dd, J = 7.5, 12.5 Hz, 1H), 2.03-2.10 (m, 1H), 2.34-2.45 (m, 2H), 3.21 (d, J = 10.5 Hz, 1H), 4.49 (dd, J = 7.2, 16.0 Hz, 1H), 5.03 (td, J = 1.0, 10.0 Hz, 1H), 5.09 (td, J = 1.0, 17.0 Hz, 1H), 5.71-5.78 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.0 (CH_3), 21.6 (CH_3), 25.2 (CH_2), 25.4 (CH_3), 27.0 (CH), 34.0 (CH_2), 41.1 (C), 43.2 (CH_2), 45.1 (CH_2), 58.7 (CH), 67.4 (CH), 113.9 (CH_2), 139.5 (CH), 172.7 (C). Lactam **2-165b**: R_f = 0.35 (100% EtOAc/hexanes); $[\alpha]_{546}^{25} +20.8$ (c 0.75, dichloromethane); IR (neat) 2959, 1644, 1412 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{23}\text{NONa}$ ($\text{M}+\text{Na}$) $^{+}$ 244.1677, found: 244.1641; ^1H NMR (500 MHz, CDCl_3) δ 0.98 (s, 3H), 1.01 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 1.43-1.53 (m, 1H), 1.58-1.70 (m, 3H), 1.75-1.82 (m, 2H), 2.03-2.12 (m, 1H), 2.39 (ddd, J = 1.0, 6.5, 14.5 Hz, 1H), 2.69 (dd, J = 2.5, 14.5 Hz, 1H), 3.25 (d, J = 11.5 Hz, 1H), 4.45 (dd, J = 6.5, 14.0 Hz, 1H), 5.05 (td, J = 1.3, 10.5 Hz, 1H), 5.13 (td, J = 1.3, 17.0 Hz, 1H), 5.79-5.86

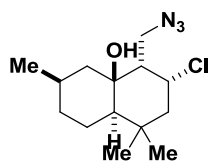
(m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 17.2 (CH_3), 23.9 (CH_3), 25.4 (CH_2), 27.1 (CH), 28.8 (CH_3), 35.5 (CH_2), 41.0 (C), 44.1 (CH_2), 44.3 (CH_2), 59.3 (CH), 69.4 (CH), 114.3 (CH_2), 140.2 (CH), 173.0 (C). The following NOE correlations were used to assign lactams **2-165a** and **2-165b**.



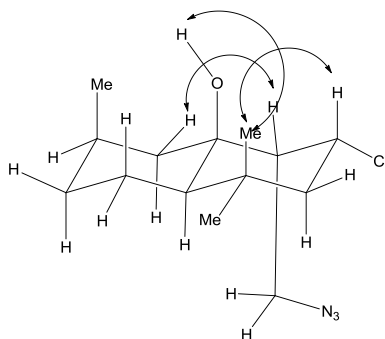
(**3R*,4R*,4aR*,6R*,8aR***)-4-(Azidomethyl)-3-chloro-1,1,6-trimethyl-decahydronaphthalen-4a-ol (**2-165c**), (**3S*,4R*,4aR*,6R*,8aR***)-4-(azidomethyl)-3-chloro-1,1,6-trimethyldecahydronaphthalen-4a-ol (**2-165d**), and (**3R*,4aR*,5R*,8aR***)-5-(azidomethyl)-3,8,8-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalen-4a-ol (**2-165e**). According to the general procedure **VI**, azides **2-164a**, **2-164b**, **2-164c**, and **2-164d** (52 mg, 0.21 mmol) afforded a mixture of lactams **2-165a** and **2-165b** (14 mg, 30%, 1:4.7 ratio) as a colorless oil, a mixture of alcohols **2-165c**, **2-165d** and **2-165e** (12 mg, 21%, 14:1:0.9 ratio) as a colorless oil, alcohol **2-165f** (2 mg, 3%) as a colorless oil, and a mixture of alcohols **2-165g** and **2-165h** (1 mg, 2%, 2.5:1 ratio) as a colorless oil after column chromatography (1-25% EtOAc/hexanes). Alcohols **2-165c**, **2-165d** and **2-165e** (14:1:0.9 ratio): R_f = 0.70 (5% EtOAc/hexanes); IR (neat) 3526, 2944, 2106 cm^{-1} ; HRMS (EI) m/z calculated for

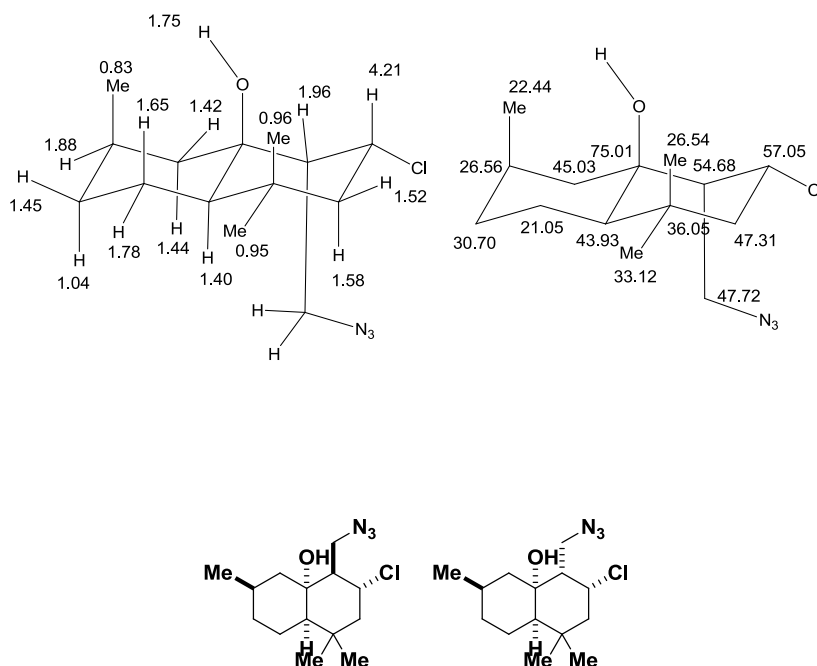
$C_{14}H_{24}ClN_3O$ (M^+) 285.1608, found: 285.1602. Alcohol **2-165c**: 1H NMR (500 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.86-0.91 (m, 1H), 0.97 (s, 3H), 1.10 (d, $J = 7.5$ Hz, 3H), 1.27-1.40 (m, 3H), 1.44 (ddd, $J = 13.2, 5.0, 4.5$ Hz, 1H), 1.51-1.66 (m, 4H), 1.95-2.01 (m, 1H), 2.05 (dd, $J = 12.9, 3.9$ Hz, 1H), 2.18 (d, $J = 1.5$ Hz, 1H), 3.76 (dd, $J = 13.1, 2.5$ Hz, 1H), 3.98 (dd, $J = 13.1, 3.2$ Hz, 1H), 4.38 (td, $J = 11.9, 4.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6 (CH_2), 20.0 (CH_3), 21.4 (CH_3), 26.4 (CH), 30.96 (CH_3), 30.98 (CH_2), 34.7 (C), 42.9 (CH_2), 47.5 (CH_2), 51.9 (CH_2), 52.1 (CH), 53.3 (CH), 56.9 (CH), 75.3 (C). Alcohol **2-165d** (diagnostic peaks only): 1H NMR (500 MHz, $CDCl_3$) δ 2.33 (d, $J = 2.5$ Hz, 1H), 3.61 (dd, $J = 12.6, 5.1$ Hz, 1H), 3.68 (dd, $J = 12.6, 10.0$ Hz, 1H), 4.58 (q, $J = 3.5$ Hz, 1H). Alcohol **2-165e** (diagnostic peaks only): 1H NMR (500 MHz, $CDCl_3$) δ 3.19 (dd, $J = 12.5, 8.5$ Hz, 1H), 4.15 (dd, $J = 8.5, 6.0$ Hz, 1H), 5.32 (dd, $J = 10.0, 1.2$ Hz, 1H), 5.55 (dd, $J = 10.0, 2.8$ Hz, 1H). The following data and NOE correlations were used to assign alcohol **2-165c**.





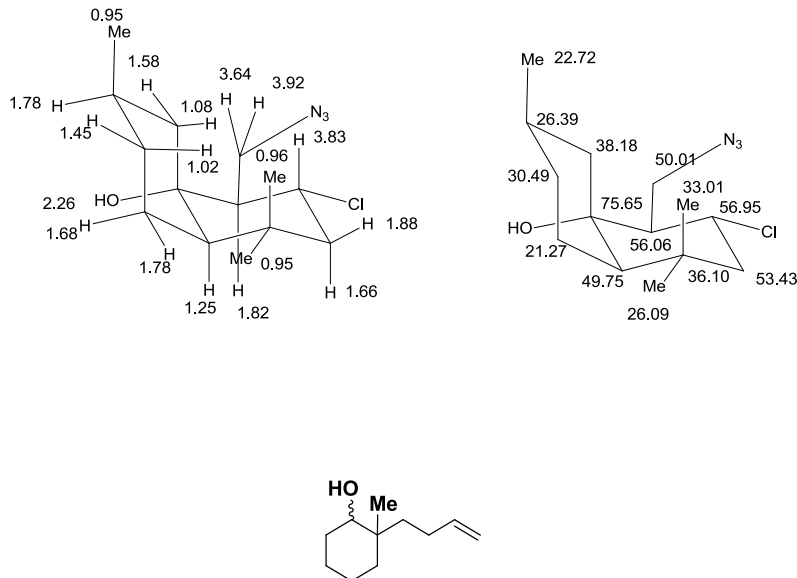
(3*R,4*S**,4*aR**,6*R**,8*aR**)-4-(Azidomethyl)-3-chloro-1,1,6-trimethyl decahydronaphthalen-4a-ol (2-165f).** Alcohol **2-165f**: $R_f = 0.45$ (50% EtOAc/hexanes); IR (neat) 3350, 2951, 2099 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.83 (d, $J = 6.6$ Hz, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 0.98-1.08 (m, 1H), 1.37-1.48 (m, 4H), 1.52 (d, $J = 12.8$ Hz, 1H), 1.56 (ddd, $J = 13.5, 4.5, 1.4$ Hz, 1H), 1.64 (dm, $J = 14.8$ Hz, 1H), 1.75 (s, 1H), 1.75-1.82 (m, 1H), 1.83-1.92 (m, 1H), 1.97 (td, $J = 4.6, 2.1$ Hz, 1H), 3.59 (dd, $J = 12.4, 6.6$ Hz, 1H), 3.68 (dd, $J = 12.4, 2.1$ Hz, 1H), 4.22 (dt, $J = 12.5, 4.3$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.1 (CH_2), 22.4 (CH_3), 26.5 (CH_3), 26.6 (CH), 30.7 (CH_2), 33.1 (CH_3), 36.1 (C), 43.9 (CH), 45.0 (CH_2), 47.3 (CH_2), 47.7 (CH_2), 54.7 (CH), 57.0 (CH), 75.0 (C). The following data and NOE correlations were used to assign alcohol **2-165f**.





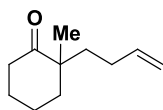
(3*R,4*R**,4*aS**,6*R**,8*aR**)-4-(Azidomethyl)-3-chloro-1,1,6-trimethyl-decahydro-naphthalen-4a-ol (2-165g)** and **(3*R**,4*S**,4*aS**,6*R**,8*aR**)-4-(azidomethyl)-3-chloro-1,1,6-trimethyldecahydronaphthalen-4a-ol (2-165h)**. Alcohol **2-165g** and **2-165h**: R_f = 0.40 (50% EtOAc/hexanes); IR (neat) 3480, 2928, 2101, 1456 cm^{-1} . Alcohol **2-165g**: ^1H NMR (500 MHz, CDCl_3) δ 0.85 (d, J = 6.5 Hz, 3H), 0.95 (s, 3H), 0.96 (s, 3H), 0.99-1.11 (m, 2H), 1.25 (dm, J = 6.5 Hz, 1H), 1.37-1.45 (m, 1H), 1.53-1.59 (m, 1H), 1.63-1.73 (m, 2H), 1.74-1.83 (m, 3H), 1.88 (dd, J = 13.0, 3.6 Hz, 1H), 2.27 (s, 1H), 3.65 (dd, J = 12.7, 8.0 Hz, 1H), 3.83 (td, J = 12.1, 3.6 Hz, 1H), 3.92 (dd, J = 12.7, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.3 (CH_2), 22.7 (CH_3), 26.1 (CH_3), 26.4 (CH), 30.5 (CH_2), 33.0 (CH_3), 36.1 (C), 38.2 (CH_2), 49.8 (CH), 50.0 (CH_2), 53.4 (CH_2), 56.1 (CH), 57.0 (CH), 75.7 (C). Alcohol **2-165h** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 0.83 (d, J = 6.5 Hz, 3H), 1.94-1.99 (m, 1H), 3.59 (dd, J = 12.5, 6.7 Hz, 1H), 3.64-3.69 (m, 1H), 4.21 (dt, J = 12.5, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.1 (CH_2), 22.4 (CH_3), 26.54 (CH or CH_3), 26.57 (CH or CH_3), 30.7 (CH_2),

33.1 (CH₃), 36.1 (C), 43.9 (CH), 45.0 (CH₂), 47.3 (CH₂), 47.7 (CH₂), 54.7 (CH), 57.0 (CH), 75.0 (C). The following data were used to assign alcohol **2-165g**.

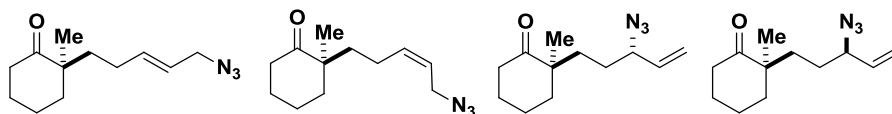


2-(But-3-enyl)-2-methylcyclohexanol. To a mixture of sodium hydride (60% in mineral oil, 880 mg, 22.0 mmol) and HMPA (5.40 g, 30.0 mmol) in THF (50 mL) at 0 °C was slowly added a solution of 2-(but-3-enyl)cyclohexanone (3.04 g, 20.0 mmol) in THF (10 mL). After 1 h, the mixture was heated to reflux for 2 h. After cooling down to 0 °C, methyl iodide (14.2 g, 100 mmol) was added slowly and then heated to reflux overnight. Diethyl ether and water were added and then the aqueous layer was extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography (0.3-0.6% EtOAc/hexanes) to afford 2-(but-3-enyl)-2-methylcyclohexanone (1.7 g, 51%, 74% brsm, 90% purity) as a colorless oil and 2-(but-3-enyl)cyclohexanone (0.94 g) as a colorless oil. According to the procedure described for the reduction of (2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone, 2-(but-3-enyl)-2-methyl-cyclohexanone (2.07 g, 12.5 mmol) afforded 2-

(but-3-enyl)-2-methylcyclohexanol (1.10 g, 52%, 1.2:1.0 ratio) as a colorless oil after column chromatography (5-7% EtOAc/hexanes). R_f = 0.15 (10% EtOAc/hexanes); IR (neat) 3368, 2929, 1640, 1450 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.90 (s, 1.4H), 0.97 (s, 1.6H), 1.02-1.21 (m, 1H), 1.25-1.63 (m, 7H), 1.67-1.77 (m, 2H), 1.98-2.09 (m, 2H), 3.40 (td, J =4.0, 10.0 Hz, 1H), 4.94 (td, J =0.8, 10.0 Hz, 1H), 5.01 (dd, J =1.2, 17.2 Hz, 1H), 5.80-5.90 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.1 (CH_3), 21.2 (CH_2), 21.3 (CH_2), 23.3 (CH_2), 24.0 (CH_3), 24.3 (CH_2), 27.5 (CH_2), 27.7 (CH_2), 29.7 (CH_2), 30.5 (CH_2), 32.4 (CH_2), 34.2 (CH_2), 35.0 (CH_2), 37.3 (C), 37.8 (C), 40.0 (CH_2), 75.8 (CH), 76.8 (CH), 113.90 (CH_2), 113.93 (CH_2), 139.7 (CH), 139.8 (CH).

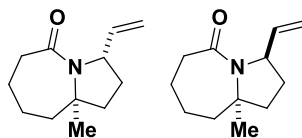


2-(But-3-enyl)-2-methylcyclohexanone. According to the general procedure for the synthesis of (2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone, 2-(but-3-enyl)-2-methylcyclohexanol (1.10 g, 6.54 mmol) afforded 2-(but-3-enyl)-2-methylcyclohexanone (0.91 g, 84%) as a colorless oil after column chromatography (0.6-1.8% EtOAc/hexanes). R_f = 0.60 (10% EtOAc/hexanes); IR (neat) 2934, 1703 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.07 (s, 3H), 1.47-1.62 (m, 2H), 1.67-1.83 (m, 6H), 1.87-1.93 (m, 2H), 1.98-2.09 (m, 1H), 2.30-2.45 (m, 2H), 4.94 (dd, J =0.8, 10.0 Hz, 1H), 5.01 (dd, J =1.6, 17.2 Hz, 1H), 5.74-5.85 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1 (CH_2), 22.5 (CH_3), 27.5 (CH_2), 28.2 (CH_2), 36.8 (CH_2), 38.8 (CH_2), 39.4 (CH_2), 48.4 (C), 114.5 (CH_2), 138.6 (CH), 215.8 (C).

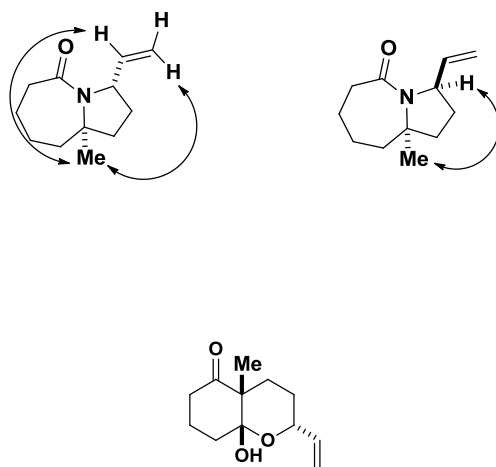


(*R,*E*)-2-(5-Azidopent-3-enyl)-2-methylcyclohexanone (2-134a), (*R**,*Z*)-2-(5-azidopent-3-enyl)-2-methylcyclohexanone (2-134b), (*R**)-2-((*S**)-3-azidopent-4-enyl)-2-methylcyclohexanone (2-134c), and (*R**)-2-((*R**)-3-azidopent-4-enyl)-2-methylcyclohexanone (2-134d).** According to general procedure **III**, 2-(but-3-enyl)-2-methylcyclohexanone (900 mg, 5.41 mmol) afforded azides **2-134a**, **2-134b**, **2-134c**, and **2-134d** (710 mg, 60%, 55:7:19:19 ratio from ^1H NMR in acetone; 55:9:18:18 ratio from ^1H NMR in CDCl_3) as a colorless oil after column chromatography (0.6-2.5% EtOAc/hexanes). Azides **2-134a**, **2-134b**, **2-134c**, and **2-134d**: R_f = 0.40 (10% EtOAc/hexanes); IR (neat) 2935, 2094, 1702, 1240 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{38}\text{N}_6\text{O}_2\text{Na}$ ($2\text{M}+\text{Na}$) $^+$ 465.2954, found: 469.2984. Azide **2-134a**: ^1H NMR (400 MHz, CDCl_3) δ 1.09 (s, 3H), 1.46-1.65 (m, 3H), 1.66-1.81 (m, 4H), 1.82-1.95 (m, 2H), 2.04-2.12 (m, 1H), 2.35-2.41 (m, 2H), 3.71 (d, J = 6.4 Hz, 2H), 5.51-5.57 (m, 1H), 5.69-5.79 (m, 1H); ^1H NMR (400 MHz, acetone) δ 1.06 (s, 3H), 1.46-1.65 (m, 3H), 1.68-1.91 (m, 7H), 2.27-2.33 (m, 1H), 2.35-2.45 (m, 1H), 3.77 (d, J = 6.6 Hz, 2H), 5.56-5.63 (m, 1H), 5.77-5.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0, 22.6, 26.7, 27.5, 37.1, 38.8, 39.3, 48.4, 52.7, 123.1 (CH), 136.5 (CH), 215.52 (C); ^{13}C NMR (100 MHz, acetone) δ 20.8 (CH_2), 22.1 (CH_3), 26.6 (CH_2), 27.3 (CH_2), 37.0 (CH_2), 38.4 (CH_2), 39.0 (CH_2), 48.0 (C), 52.3 (CH_2), 123.2 (CH), 136.4 (CH), 213.4 (C). Azide **2-134b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.10 (s, 3H), 3.77-3.82 (m, 2H); ^1H NMR (400 MHz, acetone) δ 1.08 (s, 3H), 3.90 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 47.1, 122.3 (CH), 135.7 (CH); ^{13}C NMR (100 MHz, acetone) δ 46.7 (CH_2), 122.3 (CH), 135.7 (CH). Azides **2-134c** and **2-134d** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.066 (s, 3H), 1.068 (s, 3H), 3.77-3.82 (m, 1H); 5.26-5.31 (m, 2H), 5.69-5.79 (m,

1H); ¹H NMR (400 MHz, acetone) δ 1.03 (s, 3H), 3.96 (q, *J* = 6.8 Hz, 1H), 5.29-5.36 (m, 2H), 5.77-5.86 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 65.29 (CH), 65.39 (CH), 118.31 (CH₂), 118.37 (CH₂), 135.48 (CH), 135.52 (CH), 215.40 (C), 215.47 (C); ¹³C NMR (100 MHz, acetone) δ 21.96 (CH₃), 47.78 (C), 47.81 (C), 65.21 (CH), 65.25 (CH), 117.6 (CH₂), 136.0 (CH).

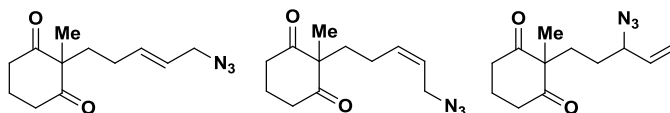
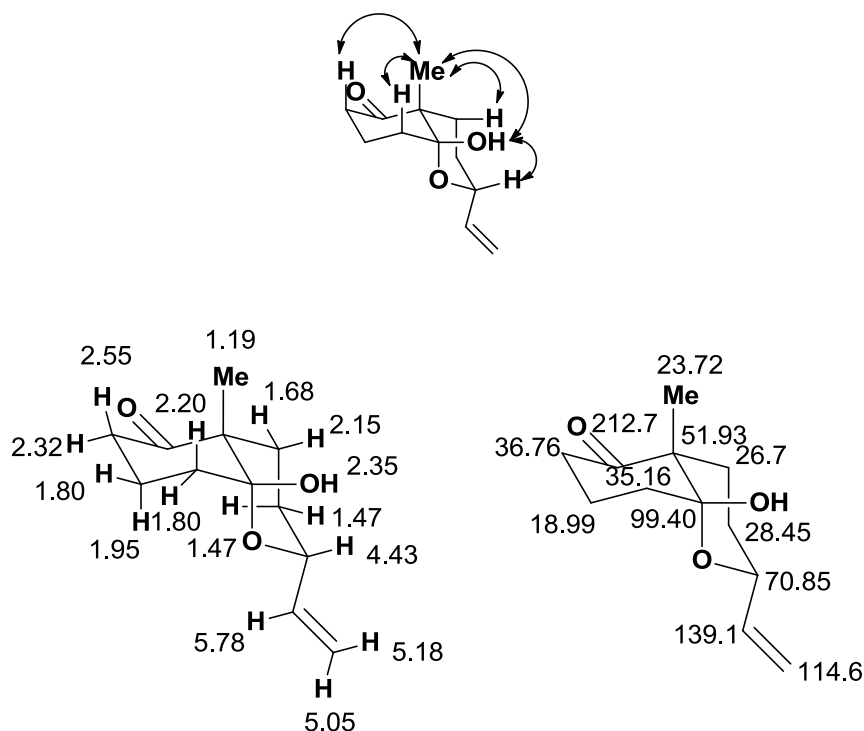


(3*S,9*aR**)-9*a*-Methyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2-135*a*)** and **(3*R**,9*aR**)-9*a*-methyl-3-vinyl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2-135*b*)**. According to the general procedure **VI**, azides **2-134*a***, **2-134*b***, **2-134*c***, and **2-134*d*** (176 mg, 0.79 mmol) afforded a mixture of lactam **2-135*a*** and lactam **2-135*b*** (115 mg, 75%, 1.1:1 ratio) as a colorless oil after column chromatography (5-35% EtOAc/hexanes). Lactams **2-135*a*** and **2-135*b***: *R_f* = 0.50 (100% EtOAc); IR (neat) 2930, 1625, 1407 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₂H₂₀NO (M+H)⁺ 194.1545, found: 194.1546; ¹H NMR (400 MHz, CDCl₃) δ 1.37 (s, 1.4H), 1.47 (s, 1.6H), 1.58-1.92 (m, 8H), 1.93-2.10 (m, 2H), 2.50-2.65 (m, 2H), 4.75-4.78 (m, 1H), 5.07-5.14 (m, 2H), 5.77-5.83 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 23.7 (CH₃), 23.9 (CH₂), 24.3 (CH₂), 25.0 (CH₂), 25.2 (CH₃), 26.7 (CH₂), 27.6 (CH₂), 37.4 (CH₂), 38.4 (CH₂), 40.3 (CH₂), 41.6 (CH₂), 42.6 (CH₂), 61.2 (CH), 62.2 (CH), 62.3 (2C), 113.5 (CH₂), 113.9 (CH₂), 138.0 (CH), 138.9 (CH), 173.3 (C), 173.5 (C). The following NOE correlations were used to assign lactams **2-135*a*** and **2-135*b***.



(2*R,4*aS**,8*aR**)-8*a*-Hydroxy-4*a*-methyl-2-vinyl-octahydrochromen-5-one (**2-84**).**

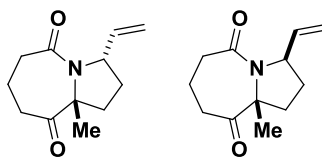
To a solution of aldehyde **83** (5.5 g, 30 mmol) in THF (50 mL) under N₂ atmosphere at -78 °C was slowly added vinyl magnesium bromide (36 mL, 1 M in THF, 36 mmol). After the addition, the mixture was stirred and allowed naturally to raise the temperature to -20 °C. Saturated aqueous ammonium chloride was added and the temperature was raised to rt. The reaction mixture extracted with ethyl acetate four times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography (6-20% EtOAc/hexanes) to afford ketone **2-84** (0.90 g, 14%) as a colorless oil. Ketone **2-84**: *R_f* = 0.55 (50% EtOAc/hexanes); IR (neat): 3422, 2944, 1701 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₂H₁₈O₃Na (M+Na)⁺ 233.1154, found: 233.1130; ¹H NMR (400 MHz, CDCl₃) δ 1.19 (s, 3H), 1.46-1.50 (m, 2H), 1.65-1.72 (m, 1H), 1.75-1.82 (m, 2H), 1.88-2.02 (m, 1H), 2.13-2.37 (m, 4H), 2.48-2.55 (m, 1H), 4.38-4.47 (m, 1H), 5.05 (dt, *J* = 1.2 Hz, 10.2 Hz, 1H), 5.19 (dt, *J* = 1.6 Hz, 17.2 Hz, 1H), 5.74-5.82 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 19.0 (CH₂), 23.7 (CH₃), 26.7 (CH₂), 28.5 (CH₂), 35.2 (CH₂), 36.8 (CH₂), 51.9 (CH₂), 70.9 (CH), 99.4 (C), 114.6 (CH₂), 139.1 (CH), 212.8 (C). The following data and NOE correlations were used to assign alcohol **2-84**.



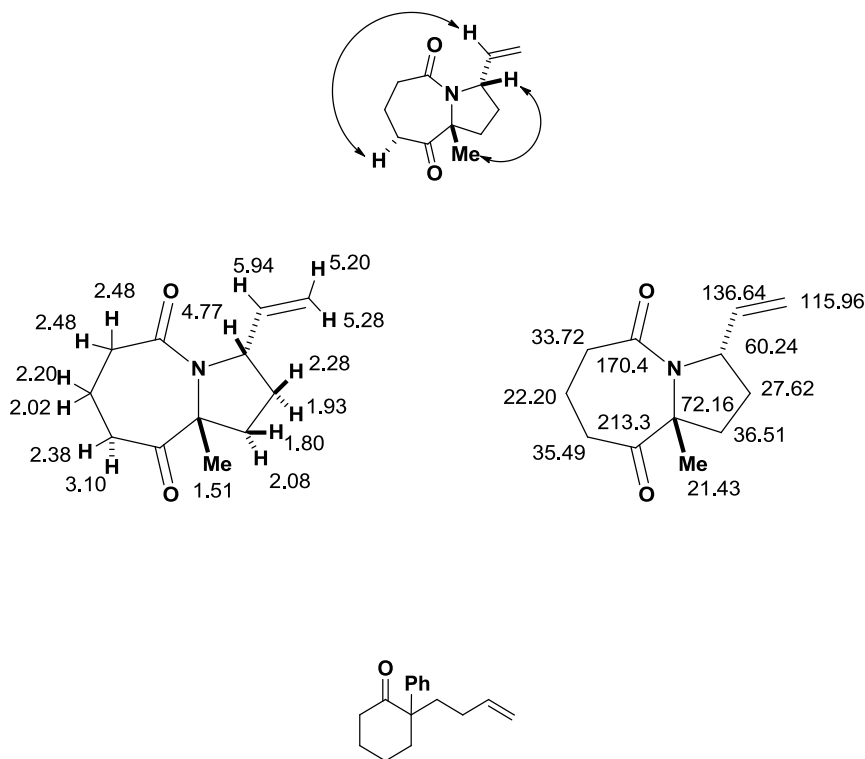
(E)-2-(5-Azidopent-3-enyl)-2-methylcyclohexane-1,3-dione (2-85a), (Z)-2-(5-azidopent-3-enyl)-2-methylcyclohexane-1,3-dione (2-85b), and 2-(3-azidopent-4-enyl)-2-methylcyclohexane-1,3-dione (2-85c). Method A: To a suspension of ketone **2-84** (370 mg, 1.76 mmol), PPh_3 (924 mg, 3.52 mmol), and $\text{Zn}(\text{N}_3)_2 \cdot 2\text{Pyr}$ (541 mmol, 1.76 mmol) in benzene (20 mL) at rt under N_2 atmosphere was slowly added DEAD (1.53 g, 40% in toluene, 3.52 mmol). The resulting mixture was heated to reflux for 24 h. The reaction was cooled to rt and the solvent was removed in vacuo. The residue was purified by chromatography (6-25% EtOAc/hexanes) to afford a mixture of azides **2-85a**, **2-85b**, and **2-85c** (270 mg, 65%, ratio:

63:6:31 from ^1H NMR in acetone; 64:6:30 from ^1H NMR in CDCl_3) as a yellow oil. Azides **2-85a**, **2-85b**, and **2-85c**: R_f = 0.60 (50% EtOAc/hexanes); IR (neat): 2934, 2100, 1726, 1695, 1245, 1026 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{35}\text{N}_4\text{O}_4$ ($2\text{M}-\text{N}_2+\text{H}$) $^+$ 443.2658, found: 443.2612. Azide **2-85a**: ^1H NMR (400 MHz, acetone) δ 1.21 (s, 3H), 1.30-1.38 (m, 1H), 1.76-2.07 (m, 5H), 2.62-2.81 (m, 4H), 3.76 (d, J = 6.4 Hz, 2H), 5.54-5.61 (m, 1H), 5.73-5.83 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 17.5 (CH_2), 19.4 (CH_3), 27.4 (CH_2), 35.9 (CH_2), 37.4 (CH_2), 37.5 (CH_2), 52.2 (CH_2), 64.7 (C), 123.9 (CH), 135.3 (CH), 209.5 (C). Azide **2-85b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 1.20 (s, 3H), 3.87 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, acetone) 64.8 (C), 123.1 (CH), 134.6 (CH). Azide **2-85c** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 1.22 (s, 3H), 3.94 (q, J = 6.8 Hz, 1H), 5.28-5.36 (m, 2H), 5.73-5.83 (m, 1H); ^{13}C NMR (100 MHz, acetone) 64.8 (CH), 117.9 (CH_2), 135.7 (CH), 209.4 (C).

Method B: To a solution of sodium azide (650 mg, 10 mmol) in deionized water (2 mL) was added benzene (10 mL). After cooling to 0 $^\circ\text{C}$, concentrated sulfuric acid (510 mg, 5 mmol, 95%) was added slowly. After stirring for 15 min, the ice bath was removed. After warming to room temperature, the organic layer was dried over anhydrous sodium sulfate. To a solution of ketone **2-84** (205 mg, 1 mmol) and triphenylphosphine (524 mg, 2 mmol) in benzene (10 mL) at 0 $^\circ\text{C}$ under N_2 atmosphere was added the above solution (2 mL, 2 mmol) and DEAD (870 mg, 40% w/w in toluene, 2 mmol) simultaneously. The reaction mixture was allowed naturally to room temperature. The solvent was removed in vacuo. The residue was purified by chromatography to afford a mixture of azides **2-85a**, **2-85b**, and **2-85c** (173 mg, 74%, ratio: 63:6:31) as a yellow oil.

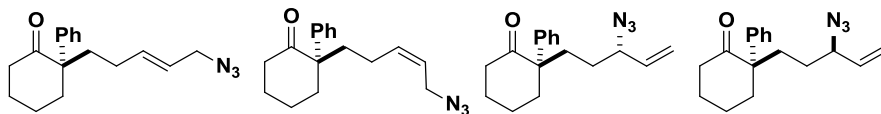


(3*S,9*aR**)-9*a*-Methyl-3-vinyl-tetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9*aH*)-dione (2-86*a*) and (3*R**,9*aR**)-9*a*-methyl-3-vinyl-tetrahydro-1*H*-pyrrolo[1,2-*a*]azepine-5,9(6*H*,9*aH*)-dione (2-86*b*)** According to the general procedure **VI**, the reaction of azide **2-85a**, **2-85b**, and **2-85c** (33 mg, 0.14 mmol) and tin tetrachloride (0.21 mL, 1 M in dichloromethane, 0.21 mmol) in anhydrous dichloromethane (3 mL) for 3 d afforded lactam **2-86a** (11 mg, 34%) as a colorless oil and lactam **2-86b** (2 mg, 7%) as a colorless oil after column chromatography (10-100% EtOAc/hexanes). Lactam **2-86a**: R_f = 0.25 (100% EtOAc/hexanes); IR (neat): 2979, 1715, 1652, 1399 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{18}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ 208.1338, found: 208.1342; ^1H NMR (400 MHz, CDCl_3) δ 1.51 (s, 1H), 1.79 (dd, J = 6.0 Hz, 12.0 Hz, 1H), 1.93 (dd, J = 6.4 Hz, 12.4 Hz, 1H), 1.99-2.13 (m, 2H), 2.14-2.30 (m, 2H), 2.34-2.54 (m, 3H), 3.12 (dd, J = 7.2 Hz, 20.8 Hz, 1H), 4.77 (t, J = 7.2 Hz, 1H), 5.19-5.30 (m, 2H), 5.89-5.97 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.4 (CH_3), 22.2 (CH_2), 27.6 (CH_2), 33.7 (CH_2), 35.5 (CH_2), 36.5 (CH_2), 60.2 (CH), 72.2 (C), 116.0 (CH_2), 136.6 (CH), 170.4 (C), 213.3 (C). Lactam **2-86b**: R_f = 0.20 (100% EtOAc/hexanes); IR (neat): 2972, 1716, 1657, 1400 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{18}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ 208.1338, found: 208.1311; ^1H NMR (400 MHz, CDCl_3) δ 1.52 (s, 3H), 1.83-2.03 (m, 4H), 2.20-2.27 (m, 2H), 2.36-2.46 (m, 3H), 2.91-2.96 (m, 1H), 4.72 (q, J = 6.8 Hz, 1H), 5.16-5.25 (m, 2H), 5.84-5.92 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5 (CH_3), 22.7 (CH_2), 29.1 (CH_2), 33.5 (CH_2), 35.2 (CH_2), 37.5 (CH_2), 61.4 (CH), 72.3 (C), 115.0 (CH_2), 138.9 (CH), 170.2 (C), 211.9 (C). The following data and NOE correlations were used to assign lactam **2-86a**.



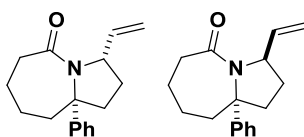
2-(But-3-enyl)-2-phenylcyclohexanone. To a mixture of sodium hydride (60% in mineral oil, 880 mg, 22.0 mmol) in THF (80 mL) at 0 °C was slowly added a solution of 2-phenylcyclohexanone (3.04 g, 20.0 mmol) in THF (15 mL). After 6 h, 4-bromobutene (10.8 g, 80.0 mmol) was added slowly at room temperature and the resulting mixture was stirred overnight. Diethyl ether and water were added and then the aqueous layer was extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by chromatography (0.3-3% EtOAc/hexanes) to afford 2-(but-3-enyl)-2-phenylcyclohexanone (1.04 g, 23%, 74% brsm) as a colorless oil and recovered 2-phenylcyclohexanone (2.42 g). R_f = 0.50 (20% EtOAc/hexanes); IR (neat) 2939, 1707, 1448 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.60-1.85 (m, 7H), 1.88-1.98 (m, 2H), 2.27-2.41 (m, 2H), 2.77 (ddd, J = 2.4, 5.6, 13.6 Hz, 1H), 4.85-4.95 (m, 2H), 5.65-5.76 (m, 1H), 7.16-7.19 (m, 2H), 7.25-7.29 (m, 1H), 7.34-7.39 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3) δ 21.7 (CH_2), 28.1 (CH_2), 28.4 (CH_2), 35.2 (CH_2), 39.3 (CH_2), 40.2 (CH_2), 57.2 (C), 114.1 (CH_2), 126.7 (CH_2), 127.0 (CH_2), 128.8 (CH_2), 138.9 (CH), 140.7 (C), 213.5 (C).



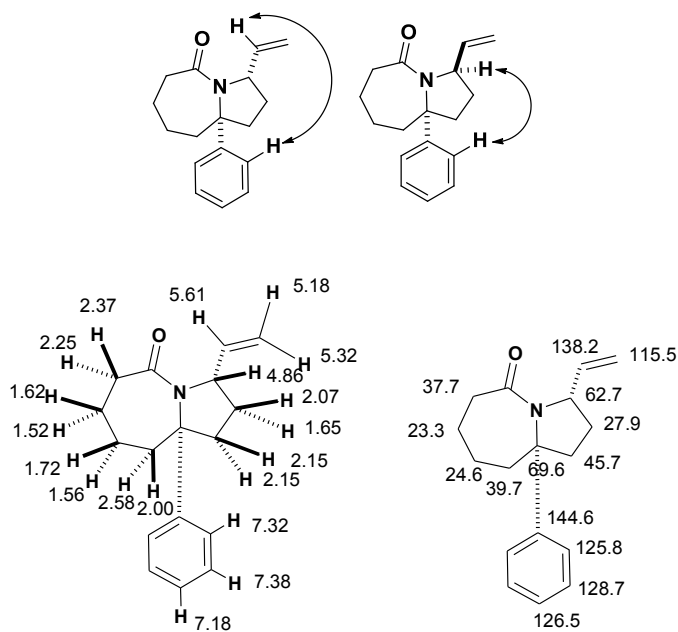
(*R,*E*)-2-(5-Azidopent-3-enyl)-2-phenylcyclohexanone (2-132a), (*R**,*Z*)-2-(5-azidopent-3-enyl)-2-phenylcyclohexanone (2-132b), (*R**)-2-((*S**)-3-azidopent-4-enyl)-2-phenylcyclohexanone (2-132c), and (*R**)-2-((*R**)-3-azidopent-4-enyl)-2-phenylcyclohexanone (2-132d).** According to the general procedure **III**, 2-(but-3-enyl)-2-phenylcyclohexanone (1.04 g, 4.60 mmol) afforded azides **2-132a**, **2-132b**, **2-132c**, and **2-132d** (680 mg, 53%, 48:8:22:22 ratio from ^1H NMR in acetone) as a colorless oil after column chromatography (0.3-1.2% EtOAc/hexanes). Azides **2-132a**, **2-132b**, **2-132c**, and **2-132d**: R_f = 0.45 (10% EtOAc/hexanes); IR (neat) 2939, 2093, 1705 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{34}\text{H}_{43}\text{N}_6\text{O}_2(2\text{M}+\text{H})^+$ 567.3447, found: 567.3425. Azide **2-132a**: ^1H NMR (400 MHz, CDCl_3) δ 1.60-1.82 (m, 7H), 1.82-1.90 (m, 1H), 1.92-2.02 (m, 1H), 2.28-2.40 (m, 2H), 2.71-2.80 (m, 1H), 3.61-3.68 (m, 2H), 5.39-5.47 (m, 1H), 5.53-5.67 (m, 1H), 7.15-7.20 (m, 2H), 7.25-7.30 (m, 1H), 7.36-7.41 (m, 2H); ^1H NMR (400 MHz, acetone) δ 1.60-1.80 (m, 7H), 1.82-1.90 (m, 1H), 1.92-1.98 (m, 1H), 2.18-2.21 (m, 1H), 2.28-2.35 (m, 1H), 2.79-2.85 (m, 1H), 3.69 (d, J = 6.6 Hz, 2H), 5.41-5.48 (m, 1H), 5.59-5.73 (m, 1H), 7.20-7.24 (m, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.7 (CH_2), 26.7 (CH_2), 28.4 (CH_2), 35.3 (CH_2), 39.5 (CH_2), 40.2 (CH_2), 52.8 (CH_2), 57.2 (C), 122.7 (CH), 126.8 (CH), 127.0 (CH), 128.9 (CH), 136.9 (CH), 140.50 (C), 213.4 (C); ^{13}C NMR (100 MHz, acetone) δ 26.6 (CH_2), 28.0 (CH_2), 34.9 (CH_2), 39.79 (CH_2), 39.85 (CH_2), 52.3 (CH_2), 57.0

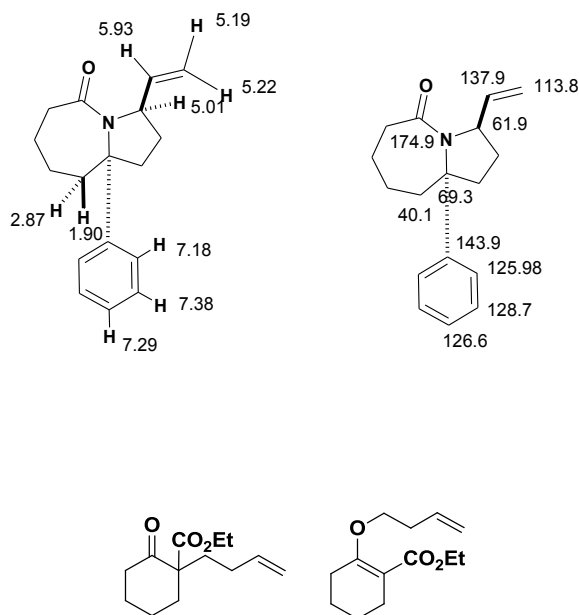
(C), 122.9 (CH), 126.7 (CH), 126.9 (CH), 128.8 (CH), 136.7 (CH), 140.9 (C), 211.51 (C). Azide **2-132b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.71-3.73 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 122.1 (CH), 135.9 (CH); ^{13}C NMR (100 MHz, acetone) δ 122.2 (CH), 135.8 (CH), 211.58 (C). Azides **2-132c** and **2-132d** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.61-3.68 (m, 1H); 5.16-5.25 (m, 2H), 5.53-5.67 (m, 1H); ^1H NMR (400 MHz, acetone) δ 3.78 (q, J = 7.2 Hz, 1H), 5.19-5.27 (m, 2H), 5.59-5.73 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 65.39 (CH), 118.21 (CH_2), 118.33 (CH_2), 135.5 (CH), 140.35 (C), 140.47 (C), 213.25 (C), 213.32 (C); ^{13}C NMR (100 MHz, acetone) δ 65.23 (CH), 65.24 (CH), 117.48 (CH_2), 117.53 (CH_2), 135.98 (CH), 136.01 (CH), 211.47 (C).



(3S*,9aR*)-9a-Phenyl-3-vinyl-hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (2-133a) and **(3R*,9aR*)-9a-phenyl-3-vinyl-hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (2-133b)**. According to the general procedure **VI**, azides **2-132a**, **2-132b**, **2-132c**, and **2-132d** (67 mg, 0.24 mmol) and titanium tetrachloride (1 M in dichloromethane, 0.36 mL, 0.36 mmol) in refluxing dichloromethane afforded lactam **2-133a** (38 mg, 63%) as a colorless oil and lactam **2-133b** (7.5 mg, 12%) as a colorless oil after column chromatography (3-8% EtOAc/hexanes). Lactam **2-133a**: R_f = 0.30 (50% EtOAc/hexanes); IR (neat) 2932, 1626, 1401 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{22}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 256.1701, found: 256.1711; ^1H NMR (400 MHz, CDCl_3) δ 1.48-1.57 (m, 2H), 1.60-1.68 (m, 2H), 1.69-1.75 (m, 1H), 1.97-2.10 (m, 2H), 2.11-2.19 (m, 2H), 2.19-2.27 (m, 1H), 2.34-2.39 (m, 1H), 2.56-2.61 (m, 1H), 4.86 (dd, J = 6.8, 12.8 Hz, 1H), 5.18 (td, J = 1.2, 10.4 Hz, 1H), 5.32 (td, J = 1.2, 17.2 Hz, 1H), 6.05 (ddd, J = 6.8, 10.4, 17.2 Hz, 1H), 7.25-7.29 (m, 2H), 7.31-7.34 (m, 1H), 7.37-7.41

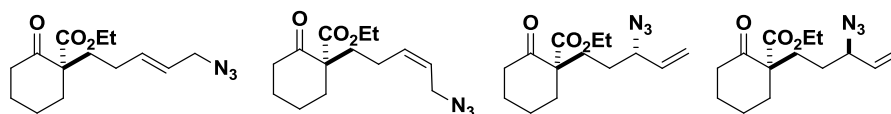
(m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.3 (CH_2), 24.6 (CH_2), 27.9 (CH_2), 37.7 (CH_2), 39.7 (CH_2), 45.7 (CH_2), 62.7 (CH), 69.6 (C), 115.5 (CH_2), 125.8 (CH), 126.5 (CH), 128.7 (CH), 138.2 (CH), 144.6 (C), 174.8 (C). Lactam **2-133b**: R_f = 0.35 (50% EtOAc/hexanes); IR (neat) 2929, 1628, 1397 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{22}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 256.1701, found: 256.1707; ^1H NMR (400 MHz, CDCl_3) δ 1.50-1.60 (m, 3H), 1.66-1.73 (m, 1H), 1.77-1.83 (m, 1H), 1.87-1.93 (m, 3H), 2.05-2.13 (m, 1H), 2.24-2.33 (m, 1H), 2.44 (dd, J = 6.8, 14.8 Hz, 1H), 2.84-2.88 (m, 1H), 5.01 (t, J = 5.6 Hz, 1H), 5.18-5.26 (m, 2H), 5.94 (ddd, J = 4.8, 10.4, 17.2 Hz, 1H), 7.19 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.6 (CH_2), 25.2 (CH_2), 25.7 (CH_2), 38.3 (CH_2), 40.1 (CH_2), 44.5 (CH_2), 61.9 (CH_2), 69.3 (C), 113.8 (CH_2), 126.0 (CH), 126.7 (CH), 128.7 (CH), 137.9 (CH), 143.9 (C), 174.9 (C). The following data and NOE correlations were used to assign lactams **2-133a** and **2-133b**.





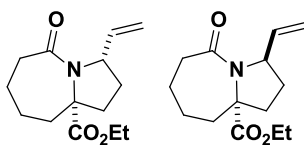
Ethyl 1-(but-3-enyl)-2-oxocyclohexanecarboxylate and **ethyl 2-(but-3-enyloxy)cyclohex-1-enecarboxylate**. To a stirred solution of t-BuOK (3.42 g, 30.5 mmol) in dry DMSO (100 mL) was slowly added ethyl 2-oxocyclohexanecarboxylate (5.16 g, 30.3 mmol) at room temperature. After 5 h, 4-bromobutene (6.03 g, 44.5 mmol) was slowly added at room temperature. After being allowed to stir overnight, diethyl ether and water were added and the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by chromatography (1.2-5% EtOAc/hexanes) to afford ethyl 1-(but-3-enyl)-2-oxocyclohexanecarboxylate (3.44 g, 51%) as a colorless oil and ethyl 2-(but-3-enyloxy)cyclohex-1-enecarboxylate (650 mg, 10%) as a colorless oil. Ethyl 1-(but-3-enyl)-2-oxocyclohexanecarboxylate: R_f = 0.20 (5% EtOAc/hexanes); IR (neat) 2939, 1710 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{20}\text{O}_3\text{Na}(\text{M}+\text{Na})^+$ 247.1310, found: 247.1316; ^1H NMR (400 MHz, CDCl_3) δ 1.26 (t, J = 7.2 Hz, 3H), 1.44 (dt, J = 4.4, 12.0 Hz, 1H), 1.57-1.78 (m, 4H), 1.92-2.08 (m, 4H), 2.38-2.53 (m, 3H), 4.19 (q, J = 7.2 Hz, 2H), 4.93 (d, J = 10.0 Hz, 1H),

5.00 (d, J = 17.2 Hz, 1H), 5.72-5.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (CH_3), 22.6 (CH_2), 27.6 (CH_2), 28.6 (CH_2), 33.9 (CH_2), 36.1 (CH_2), 41.1 (CH_2), 60.5 (C), 61.1 (CH_2), 114.7 (CH_2), 138.0 (CH), 171.9 (C), 207.7 (C). Ethyl 2-(but-3-enyloxy)cyclohex-1-enecarboxylate: R_f = 0.15 (5% EtOAc/hexanes); IR (neat) 2936 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{21}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 225.1491, found: 225.1482; ^1H NMR (400 MHz, CDCl_3) δ 1.29 (t, J = 7.2 Hz, 3H), 1.55-1.61 (m, 2H), 1.66-1.72 (m, 2H), 2.26-2.33 (m, 4H), 2.43 (q, J = 6.8 Hz, 2H), 3.90 (t, J = 6.8 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 5.07 (d, J = 10.4 Hz, 1H), 5.12 (dd, J = 1.2, 17.2 Hz, 1H), 5.84-5.92 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.4 (CH_3), 22.1 (CH_2), 22.5 (CH_2), 25.4 (CH_2), 26.7 (CH_2), 34.3 (CH_2), 59.8 (CH_2), 67.7 (CH_2), 108.8 (C), 116.8 (CH_2), 134.6 (CH), 161.3 (C), 168.1 (C).



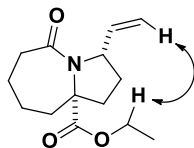
(S^* , E)-Ethyl 1-(5-azidopent-3-enyl)-2-oxocyclohexanecarboxylate (**2-136a**), (S^* , Z)-ethyl 1-(5-azidopent-3-enyl)-2-oxocyclohexanecarboxylate (**2-136b**), (S^*)-ethyl 1-((S^*)-3-azidopent-4-enyl)-2-oxocyclohexanecarboxylate (**2-136c**), and (S^*)-ethyl 1-((R^*)-3-azidopent-4-enyl)-2-oxocyclohexanecarboxylate (**2-136d**). According to the general procedure **III**, ethyl 1-(but-3-enyl)-2-oxocyclohexanecarboxylate (2.24 g, 10.0 mmol) afforded azides **2-136a**, **2-136b**, **2-136c**, and **2-136d** (1.33 g, 48%, 68% brsm, 59:7:17:17 from ^1H NMR in acetone; 63:7:15:15 from ^1H NMR in CDCl_3) as a colorless oil and ethyl 1-(but-3-enyl)-2-oxocyclohexanecarboxylate (650 mg) after column chromatography (0.6-3% EtOAc/hexanes). Azides **2-136a**, **2-136b**, **2-136c**, and **2-136d**: R_f = 0.20 (10% EtOAc/hexanes); IR (neat) 2940, 2095, 1709 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{28}\text{H}_{42}\text{N}_6\text{O}_6\text{Na}$ ($2\text{M}+\text{Na}$) $^+$ 581.3064, found: 581.3050. Azide **2-136a**: ^1H NMR (500 MHz,

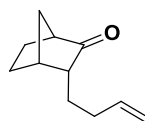
CDCl₃) δ 1.29 (t, J = 7.0 Hz, 3H), 1.41-1.51 (m, 1H), 1.58-1.72 (m, 4H), 1.73-1.82 (m, 1H), 1.92-2.13 (m, 3H), 2.43-2.57 (m, 3H), 3.71 (d, J = 6.5 Hz, 2H), 4.20-4.25 (m, 2H), 5.51-5.59 (m, 1H), 5.70-5.79 (m, 1H); ¹H NMR (500 MHz, acetone) δ 1.24-1.28 (m, 3H), 1.47-1.58 (m, 1H), 1.58-1.78 (m, 4H), 1.82-2.11 (m, 4H), 2.31-2.36 (m, 1H), 2.47-2.55 (m, 2H), 3.77 (d, J = 6.5 Hz, 2H), 4.20-4.25 (m, 2H), 5.56-5.62 (m, 1H), 5.76-5.85 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (CH₃), 22.6 (CH₂), 27.2 (CH₂), 27.6 (CH₂), 34.2 (CH₂), 36.3 (CH₂), 41.1 (CH₂), 52.7 (CH₂), 60.53 (C), 61.3 (CH₂), 123.3 (CH), 135.9 (CH), 171.87 (C), 207.82 (C); ¹³C NMR (125 MHz, acetone) δ 14.4 (CH₃), 23.3 (CH₂), 28.0 (CH₂), 28.2 (CH₂), 35.1 (CH₂), 36.85 (CH₂), 41.6 (CH₂), 53.1 (CH₂), 61.16 (C), 61.77 (CH₂), 124.4 (CH), 136.76 (CH), 172.41 (C), 207.24 (C). Azide **2-136b** (diagnostic peaks only): ¹H NMR (500 MHz, acetone) δ 3.90 (d, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 60.56 (C), 122.8 (CH), 135.0 (CH), 171.92 (C), 207.89 (C); ¹³C NMR (125 MHz, acetone) δ 61.22 (C), 123.7 (CH), 136.0 (CH), 172.45 (C), 207.38 (C). Azides **2-136c** and **2-136d** (diagnostic peaks only): ¹H NMR (500 MHz, CDCl₃) δ 3.79-3.84 (m, 1H); 5.28-5.31 (m, 2H), 5.70-5.77 (m, 1H); ¹H NMR (500 MHz, acetone) δ 3.97 (q, J = 7.0 Hz, 1H), 5.30 (d, J = 10.2 Hz, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.77-5.85 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 60.36 (C), 60.40 (C), 65.06 (CH), 65.11 (CH), 118.51 (CH₂), 118.56 (CH₂), 135.29 (CH), 135.33 (CH₂), 171.84 (C), 207.69 (C); ¹³C NMR (125 MHz, acetone) δ 61.0 (C), 65.83 (CH), 65.86 (CH), 118.7 (CH₂), 136.71 (CH), 136.76 (CH), 207.18 (C), 207.27 (C).



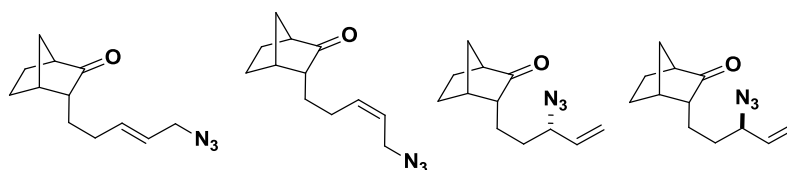
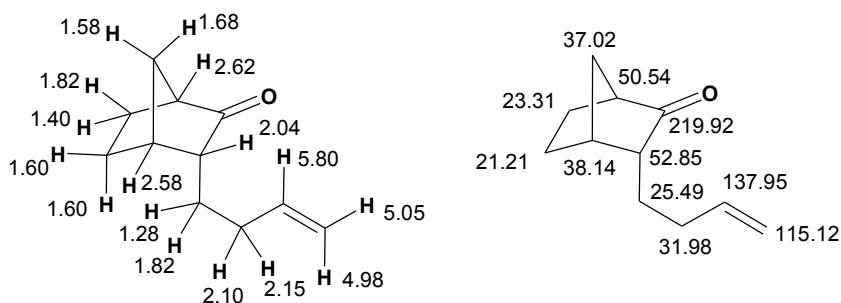
(**3S***,**9aR***)-Ethyl 5-oxo-3-vinyl-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-9a-carboxylate (**2-137a**) and (**3R***,**9aR***)-Ethyl 5-oxo-3-vinyl-octahydro-1*H*-pyrrolo[1,2-

a)azepine-9a-carboxylate (2-137b). According to the general procedure **VI**, azides **2-136a**, **2-136b**, **2-136c**, and **2-136d** (185 mg, 0.66 mmol) and titanium chloride in refluxing dichloroethane afforded lactam **2-137a** (57 mg, 36%) as a colorless oil and lactam **2-137b** (34 mg, 20%) as a colorless oil after column chromatography (10-40% EtOAc/hexanes). Lactam **2-137a**: R_f = 0.20 (50% EtOAc/hexanes); IR (neat) 2934, 1734, 1638, 1400 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{21}\text{NO}_3\text{Na}$ ($\text{M}+\text{Na}$) $^{+}$ 274.1419, found: 274.1419; ^1H NMR (400 MHz, CDCl_3) δ 1.31 (t, J = 7.2 Hz, 3H), 1.42-1.62 (m, 2H), 1.63-1.78 (m, 3H), 1.82-1.90 (m, 1H), 1.98-2.10 (m, 2H), 2.32-2.45 (m, 3H), 2.53 (dd, J = 6.8, 14.4 Hz, 1H), 4.20-4.31 (m, 2H), 4.80 (br, 1H), 5.10 (td, J = 1.2, 10.4 Hz, 1H), 5.29 (td, J = 1.2, 17.2 Hz, 1H), 5.84 (ddd, J = 5.6, 10.4, 17.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2 (CH_3), 22.9 (CH_2), 26.6 (CH_2), 28.2 (CH_2), 38.0 (CH_2), 38.2 (CH_2), 40.2 (CH_2), 61.5 (CH_2), 62.4 (CH), 69.3 (C), 114.8 (CH_2), 137.7 (CH), 173.5 (C), 174.2 (C). Lactam **2-137b**: R_f = 0.26 (50% EtOAc/hexanes); IR (neat) 2933, 1730, 1638, 1394 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{21}\text{NO}_3\text{Na}$ ($\text{M}+\text{Na}$) $^{+}$ 274.1419, found: 274.1400; ^1H NMR (400 MHz, CDCl_3) δ 1.31 (t, J = 7.2 Hz, 3H), 1.48-1.60 (m, 3H), 1.63 (dd, J = 6.0, 12.4 Hz, 1H), 1.76-1.83 (m, 1H), 1.86-1.92 (m, 1H), 1.93-2.02 (m, 1H), 2.13 (dt, J = 6.0, 13.2 Hz, 1H), 2.22-2.30 (m, 2H), 2.57-2.65 (m, 2H), 4.20-4.32 (m, 2H), 4.90 (dd, J = 4.8, 8.0 Hz, 1H), 5.10-5.15 (m, 2H), 5.84 (ddd, J = 4.6, 10.0, 17.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3 (CH_3), 23.0 (CH_2), 26.8 (CH_2), 26.9 (CH_2), 38.2 (CH_2), 38.5 (CH_2), 40.1 (CH_2), 61.4 (CH), 61.7 (CH_2), 69.7 (C), 113.8 (CH_2), 137.8 (CH), 173.3 (C), 174.4 (C). The following NOE correlation was used to assign lactams **2-137a**.





(1*S,3*R**,4*R**)-3-(But-3-enyl)bicyclo[2.2.1]heptan-2-one.** A solution of 3-methylene-2-norbornanone (2.45 g, 20.0 mmol) in dichloromethane (60 mL) was stirred at -78 °C as titanium tetrachloride (neat, 20 mL, 1 M in dichloromethane, 20 mmol) was added dropwise over 5 min to form a gray solution. After stirring 40 min, a solution of allyltrimethylsilane (2.97 g, 26.0 mmol) in dichloromethane (30 mL) was added dropwise over 5 min. The resulting purple solution was stirred at -78 °C for 30 min and at 0 °C for an additional 20 min. A solution of triethylamine (15 mL) and methanol (5 mL) was added dropwise over 5 min, forming a white heterogeneous mixture that was diluted with diethyl ether (100 mL) and filtered. The mixture was washed with 10% HCl, saturated aqueous sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a crude product, which was purified by chromatography (0.6-5% EtOAc/hexanes) to afford (1*S**,3*R**,4*R**)-3-(but-3-enyl)bicyclo[2.2.1]heptan-2-one (1.20 g, 36%) as a colorless oil. R_f = 0.3 (10% EtOAc/hexanes); IR (neat) 2961, 1740 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{16}\text{ONa}$ ($\text{M}+\text{Na}$)⁺ 187.1099, found: 187.1122; ^1H NMR (400 MHz, CDCl_3) δ 1.25-1.35 (m, 1H), 1.36-1.45 (m, 1H), 1.57-1.62 (m, 3H), 1.67 (d, J = 10.0 Hz, 1H), 1.75-1.87 (m, 2H), 2.00-2.21 (m, 3H), 2.60 (br, 2H), 4.98 (td, J = 0.8, 10.4 Hz, 1H), 5.04 (qd, J = 1.6, 17.2 Hz, 1H), 5.79 (tdd, J = 6.6, 10.4, 17.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1 (CH_2), 25.3 (CH_2), 25.5 (CH_2), 32.0 (CH_2), 37.0 (CH_2), 38.1 (CH), 50.5 (CH), 52.8 (CH), 115.1 (CH_2), 137.9 (CH), 219.9 (C). The following data were used to assign the title ketone.



(1*S*^{*},3*R*^{*},4*R*^{*},*E*)-3-(5-Azidopent-3-enyl)bicyclo[2.2.1]heptan-2-one (2-142a),

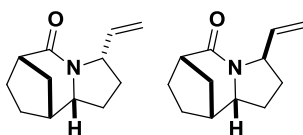
(1*S*^{*},3*R*^{*},4*R*^{*},*Z*)-3-(5-azidopent-3-enyl)bicyclo[2.2.1]heptan-2-one (2-142b),

(1*S*^{*},3*R*^{*},4*R*^{*})-3-((*S*^{*})-3-azidopent-4-enyl)bicyclo[2.2.1]heptan-2-one (2-142c) and

(1*S*^{*},3*R*^{*},4*R*^{*})-3-((*R*^{*})-3-azidopent-4-enyl)bicyclo[2.2.1]heptan-2-one (2-142d).

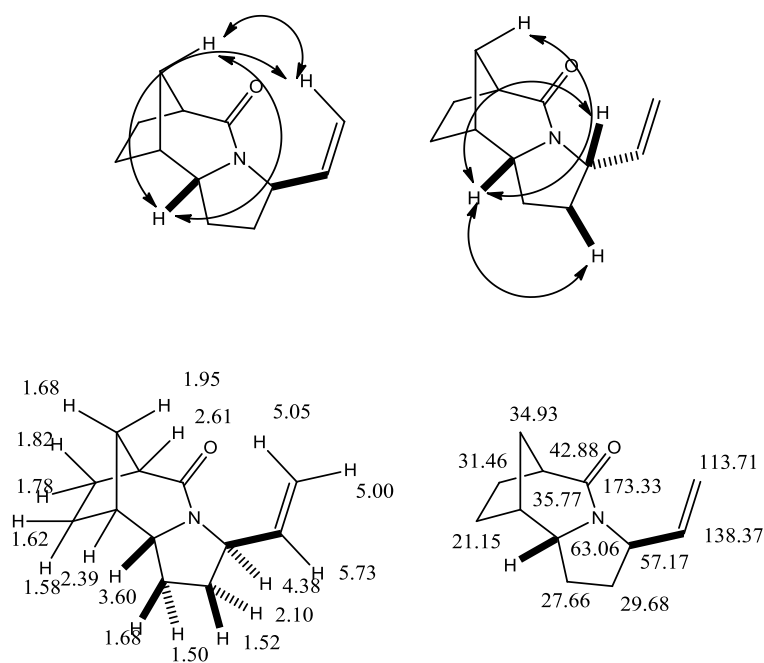
According to the general procedure **III**, (1*S*^{*},3*R*^{*},4*R*^{*})-3-(but-3-enyl)bicyclo[2.2.1]heptan-2-one (1.10 g, 6.70 mmol) afforded azides **2-142a**, **2-142b**, **2-142c**, and **2-142d** (1.30 g, 89%, 63:7:15:15 ratio from ¹H NMR in acetone; 68:8:12:12 from ¹H NMR in CDCl₃) as a colorless oil after column chromatography (0.6-5% EtOAc/hexanes). Azides **2-142a**, **2-142b**, **2-142c**, and **2-142d**: *R_f* = 0.3 (10% EtOAc/hexanes); IR (neat) 2957, 2093, 1739 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₂H₁₇N₃ONa (M + Na)⁺ 242.1269, found: 242.1299. Azide **2-142a**: ¹H NMR (500 MHz, CDCl₃) δ 1.28-1.49 (m, 5H), 1.52-1.68 (m, 2H), 1.70-1.80 (m, 3H), 2.10-2.22 (m, 1H), 2.34 (br, 1H), 2.47 (br, 1H), 3.63 (d, *J* = 6.5 Hz, 2H), 5.46-5.52 (m, 1H), 5.64-5.70 (m, 1H); ¹H NMR (500 MHz, acetone) δ 1.28-1.47 (m, 3H), 1.49 (d, *J* = 11.5 Hz, 1H), 1.55-1.65 (m, 1H), 1.67-1.73 (m, 2H), 1.77-1.88 (m, 3H), 2.18-2.32 (m, 1H), 2.42 (br, 1H),

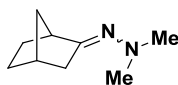
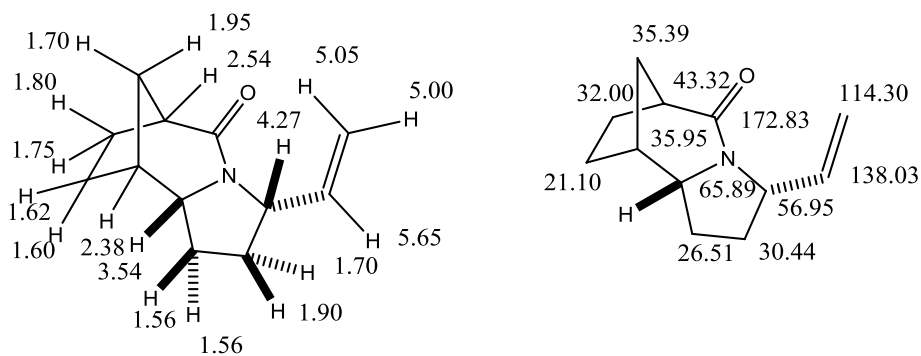
2.46 (br, 1H), 3.78 (d, J = 6.5 Hz, 2H), 5.59-5.65 (m, 1H), 5.78-5.86 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 24.0 (CH_2), 27.9 (CH_2), 28.5 (CH_2), 30.7 (CH_2), 34.84 (CH_2), 39.2 (CH), 49.6 (CH), 52.7 (CH_2), 53.0 (CH), 123.8 (CH), 135.8 (CH), 220.1 (C); ^{13}C NMR (125 MHz, acetone) δ 24.5 (CH_2), 28.6 (CH_2), 29.4 (CH_2), 31.3 (CH_2), 35.19 (CH_2), 40.0 (CH), 50.15 (CH), 53.2 (CH_2), 53.5 (CH), 124.8 (CH), 136.7 (CH), 218.6 (C). Azide **2-142b** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 3.71-3.82 (m, 2H); ^1H NMR (500 MHz, acetone) δ 3.88-3.97 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 123.1 (CH), 135.0 (CH), 219.9 (C); ^{13}C NMR (125 MHz, acetone) δ 124.0 (CH), 136.0 (CH). Azides **2-142c** and **2-142d** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 3.71-3.82 (m, 1H), 5.18-5.23 (m, 2H), 5.64-5.70 (m, 1H); ^1H NMR (500 MHz, acetone) δ 4.01 (d, J = 7.0 Hz, 1H), 5.30 (d, J = 10.0 Hz, 1H), 5.34 (d, J = 17.0 Hz, 1H), 5.74-5.85 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 64.8 (CH), 65.0 (CH), 118.4 (CH_2), 118.5 (CH_2), 135.3 (CH), 135.5 (CH), 219.56 (C), 219.64 (C); ^{13}C NMR (125 MHz, acetone) δ 65.60 (CH), 65.63 (CH), 118.58 (CH_2), 118.63 (CH_2), 136.85 (CH), 136.93 (CH), 218.33 (C), 218.30 (C).



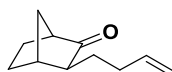
(**1S*,2S*,5R*,8S***)-5-Vinyl-6-azatricyclo[6.1.2.0^{2,6}]undecan-7-one (**2-143a**) and (**1S*,2S*,5S*,8S***)-5-vinyl-6-azatricyclo[6.1.2.0^{2,6}]undecan-7-one (**2-143b**). According to the general procedure **VI**, azides **2-142a**, **2-142b**, **2-142c**, and **2-142d** (130 mg, 0.593 mmol) afforded lactam **2-143a** (69 mg, 61%) as a colorless oil and **2-143b** (5 mg, 4%) as a colorless oil after column chromatography (11-35% EtOAc/hexanes). Lactam **2-143a**: R_f = 0.15 (100% EtOAc/hexanes); IR (neat) 2946, 1644, 1418 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{17}\text{NONa}$ ($\text{M}+\text{Na}$)⁺ 214.1208, found: 214.1232; ^1H NMR (500 MHz, CDCl_3) δ 1.55-1.65

(m, 4H), 1.67-1.73 (m, 2H), 1.73-1.83 (m, 2H), 1.87-1.93 (m, 1H), 1.95 (dd, $J = 1.0$, 11.5 Hz, 1H), 2.38 (br, 1H), 2.54 (dt, $J = 0.8$, 4.5 Hz, 1H), 3.52-3.56 (m, 1H), 4.27 (t, $J = 7.5$ Hz, 1H), 5.00 (td, $J = 1.0$, 10.5 Hz, 1H), 5.05 (td, $J = 1.0$, 17.0 Hz, 1H), 5.65 (ddd, $J = 6.5$, 10.5, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.4 (CH_2), 26.5 (CH_2), 30.4 (CH_2), 32.0 (CH_2), 35.4 (CH_2), 36.0 (CH), 43.3 (CH), 56.9 (CH), 65.9 (CH), 114.3 (CH_2), 138.0 (CH), 172.8 (C). Lactam **2-143b**: $R_f = 0.2$ (100% EtOAc/hexanes); IR (neat) 2950, 1645, 1428 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{17}\text{NONa}$ ($\text{M}+\text{Na}$) $^+$ 214.1208, found: 214.1233; ^1H NMR (500 MHz, CDCl_3) δ 1.45-1.62 (m, 4H), 1.65-1.71 (m, 2H), 1.72-1.85 (m, 2H), 1.95 (d, $J = 11.5$ Hz, 1H), 2.07-2.11 (m, 1H), 2.39 (br, 1H), 2.61 (t, $J = 4.5$ Hz, 1H), 3.57-3.62 (m, 1H), 4.38 (dd, $J = 6.5$, 13.5 Hz, 1H), 5.00 (td, $J = 1.5$, 10.0 Hz, 1H), 5.05 (td, $J = 1.3$, 17.0 Hz, 1H), 5.73 (ddd, $J = 5.5$, 10.5, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.1 (CH_2), 27.7 (CH_2), 29.7 (CH_2), 31.5 (CH_2), 34.9 (CH_2), 35.8 (CH), 42.9 (CH), 57.2 (CH), 63.1 (CH), 113.7 (CH_2), 138.4 (CH), 173.3 (C). The following data and NOE correlations were used to assign lactams **2-143a** and **2-143b**.

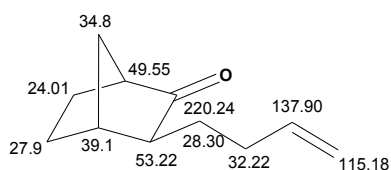
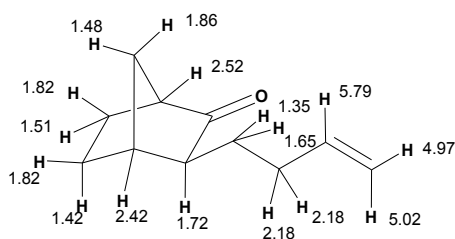


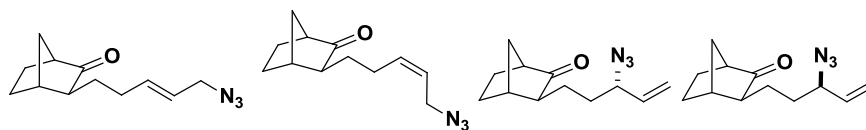


2-(Bicyclo[2.2.1]heptan-2-ylidene)-1,1-dimethylhydrazine. According to the general procedure **IV**, 2-norbornanone (6.6 g, 60 mmol) and 1,1-dimethylhydrazine (12 g, 0.18 mol) afforded 2-(bicyclo[2.2.1]heptan-2-ylidene)-1,1-dimethylhydrazine (27.3 g, 100%, E/Z: 4:1), which was used without purification. IR (neat) 2952, 1669, 1466 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_9\text{H}_{17}\text{N}_2$ ($\text{M}+\text{H}$)⁺ 153.1392, found: 153.1382. Major isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.25-1.50 (m, 4H), 1.62-1.78 (m, 2H), 2.05 (dd, $J=3.0, 17.2$ Hz, 1H), 2.25 (d, $J=17.2$ Hz, 1H), 2.44 (s, 6H), 2.47-2.50 (m, 1H), 2.78 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.9 (CH_2), 27.73 (CH_2), 35.7 (CH), 36.9 (CH_2), 38.2 (CH_2), 44.9 (CH), 47.1 (CH_3), 176.5 (C). Minor isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.94 (dd, $J=3.0, 16.4$ Hz, 1H), 3.36 (br, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.2 (CH_2), 27.67 (CH_2), 34.9 (CH), 38.4 (CH_2), 39.5 (CH_2), 40.8 (CH), 48.0 (CH_3), 176.1 (C).



(1S*,3S*,4R*)-3-(But-3-enyl)bicyclo[2.2.1]heptan-2-one. According to the general procedure V, 2-(bicyclo[2.2.1]heptan-2-ylidene)-1,1-dimethylhydrazine (4.56 g, 30.0 mmol), n-BuLi (12 mL, 2.5 M in hexane, 30 mmol) and 4-bromo-1-butene (4.5 g, 33 mmol) afforded (1S*,3S*,4R*)-3-(but-3-enyl)bicyclo[2.2.1]heptan-2-one (3.68 g, 75%) as a colorless oil after column chromatography (0.6-11% EtOAc/hexanes). $R_f = 0.60$ (10% EtOAc/hexanes); IR (neat) 2958, 1740 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{17}\text{O}$ ($\text{M}+\text{H}$) $^{+}$ 165.1279, found: 165.1242; ^1H NMR (400 MHz, CDCl_3) δ 1.28-1.38 (m, 1H), 1.38-1.53 (m, 3H), 1.60-1.68 (m, 1H), 1.68-1.75 (m, 1H), 1.78-1.87 (m, 3H), 2.08-2.25 (m, 2H), 2.42 (br, 1H), 2.53 (br, 1H), 4.97 (td, $J = 0.8, 10.0$ Hz, 1H), 5.03 (qd, $J = 1.6, 17.2$ Hz, 1H), 5.78 (tdd, $J = 6.6, 10.4, 17.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.0 (CH_2), 27.9 (CH_2), 28.3 (CH_2), 32.2 (CH_2), 34.8 (CH_2), 39.1 (CH), 49.6 (CH), 53.2 (CH), 115.2 (CH_2), 137.9 (CH), 220.2 (C). The following data were used to assign the title ketone.





(1*S*^{*},3*S*^{*},4*R*^{*},*E*)-3-(5-Azidopent-3-enyl)bicyclo[2.2.1]heptan-2-one (2-140a),

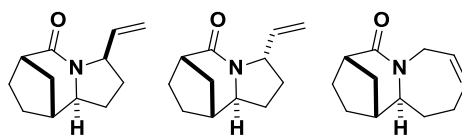
(1*S*^{*},3*S*^{*},4*R*^{*},*Z*)-3-(5-azidopent-3-enyl)bicyclo[2.2.1]heptan-2-one (2-140b),

(1*S*^{*},3*S*^{*},4*R*^{*})-3-((*S*^{*})-3-azidopent-4-enyl)bicyclo[2.2.1]heptan-2-one (2-140c) and

(1*S*^{*},3*S*^{*},4*R*^{*})-3-((*R*^{*})-3-azidopent-4-enyl)bicyclo[2.2.1]heptan-2-one (2-140d).

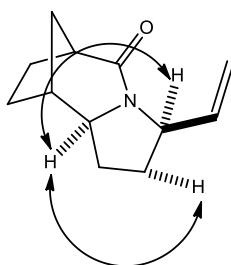
According to the general procedure **III**, (1*S*^{*},3*S*^{*},4*R*^{*})-3-(but-3-enyl)bicyclo[2.2.1]heptan-2-one (1.50 g, 9.10 mmol), HG-2 (285 mg, 0.450 mmol) and allyl bromide (3.9 mL, 45.5 mmol) afforded a mixture of azides **2-140a**, **2-140b**, **2-140c**, and **2-140d** (1.77 g, 84%, 64:8:14:14 ratio from ¹H NMR in acetone; 68:8:12:12 from ¹H NMR in CDCl₃) as a colorless oil after column chromatography (0.6-6% EtOAc/hexanes). Azides **2-140a**, **2-140b**, **2-140c**, and **2-140d**: *R*_f = 0.25 (10% EtOAc/hexanes); IR (neat) 2959, 2093, 1739, 1239 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₂H₁₇N₃ONa (M + Na)⁺ 242.1269, found: 242.1295. Azide **2-140a**: ¹H NMR (500 MHz, CDCl₃) δ 1.27-1.35 (m, 1H), 1.37-1.43 (m, 1H), 1.52-1.63 (m, 3H), 1.67 (dd, *J* = 1.0, 10.0 Hz, 1H), 1.75-1.85 (m, 2H), 1.95-2.05 (m, 1H), 2.08-2.23 (m, 2H), 2.60 (br, 2H), 3.70 (d, *J* = 6.5 Hz, 2H), 5.53-5.59 (m, 1H), 5.69-5.76 (m, 1H); ¹H NMR (500 MHz, acetone) δ 1.23-1.32 (m, 2H), 1.53-1.60 (m, 4H), 1.62-1.72 (m, 2H), 1.75-1.82 (m, 1H), 1.97-2.03 (m, 1H), 2.08-2.22 (m, 1H), 2.43 (d, *J* = 5.0 Hz, 1H), 2.59 (br, 1H), 3.73 (d, *J* = 5.5 Hz, 2H), 5.56-5.62 (m, 1H), 5.73-5.83 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 21.1 (CH₂), 25.3 (CH₂), 25.6 (CH₂), 30.5 (CH₂), 37.0 (CH₂), 38.2 (CH), 50.5 (CH), 52.69 (CH), 52.74 (CH₂), 123.7 (CH), 135.9 (CH), 219.8 (C); ¹³C NMR (125 MHz, acetone) δ 21.7 (CH₂), 25.9 (CH₂), 26.7 (CH₂), 31.2 (CH₂), 37.4 (CH₂), 39.0 (CH), 51.1 (CH), 53.17 (CH₂), 53.20 (CH), 124.7 (CH), 136.83 (CH), 218.3 (C). Azide **2-140b** (diagnostic peaks only): ¹H NMR (500 MHz,

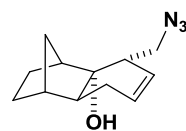
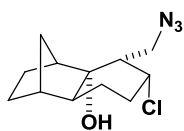
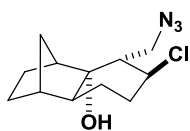
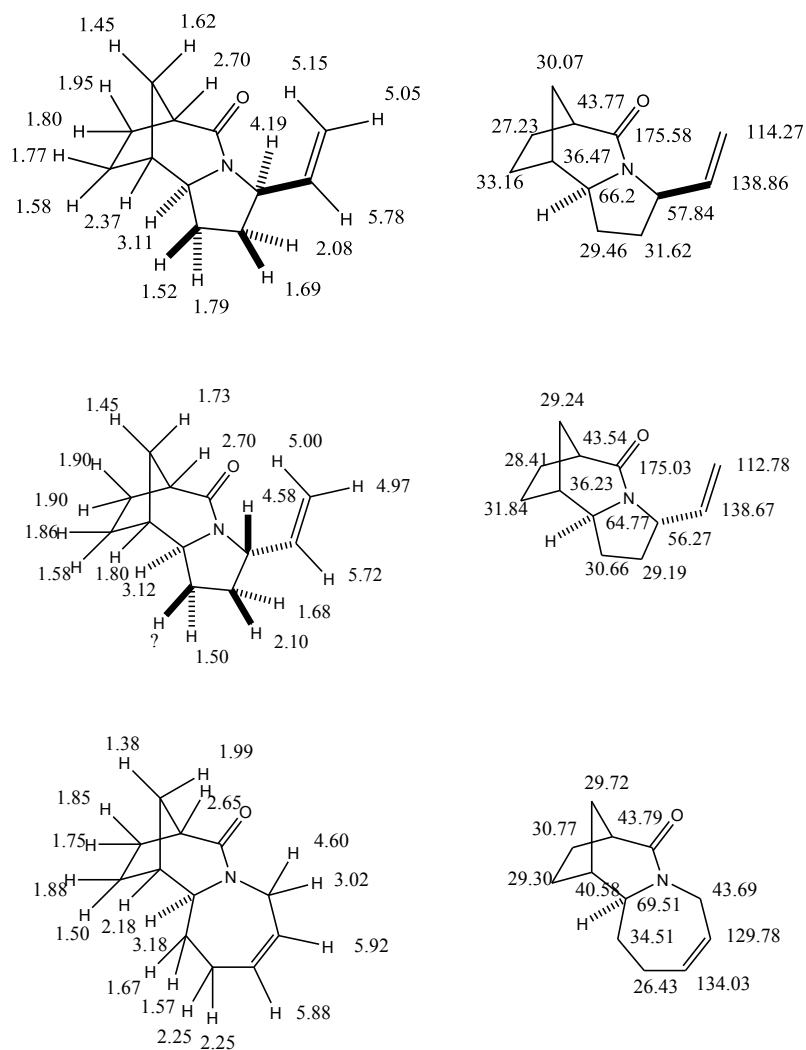
CDCl₃) δ 3.79-3.86 (m, 2H); ¹H NMR (500 MHz, acetone) δ 3.88 (d, J = 7.5 Hz, 2H), 5.50-5.56 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 123.0 (CH), 135.2 (CH), 219.6 (C); ¹³C NMR (125 MHz, acetone) δ 123.8 (CH), 136.1 (CH). Azides **2-140c** and **2-140d** (diagnostic peaks only): ¹H NMR (500 MHz, CDCl₃) δ 3.79-3.86 (m, 1H), 5.26-5.29 (m, 2H), 5.70-5.77 (m, 1H); ¹H NMR (500 MHz, acetone) δ 3.96-4.01 (m, 1H), 5.25 (ddd, J = 0.7, 1.3, 11.0 Hz, 1H), 5.31 (td, J = 1.1, 17.0 Hz, 1H), 5.72-5.82 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 64.9 (CH), 65.0 (CH), 118.4 (CH₂), 118.7 (CH₂), 135.3 (CH), 135.5 (CH), 219.26 (C), 219.35 (C); ¹³C NMR (125 MHz, acetone) δ 65.65 (CH), 65.70 (CH), 118.55 (CH₂), 118.69 (CH₂), 136.85 (CH), 136.99 (CH), 218.00 (C), 218.05 (C).



(1*S**,2*R**,5*S**,8*S**)-5-Vinyl-6-azatricyclo[6.1.2.0^{2,6}]undecan-7-one (**2-141a**),
 (1*S**,2*R**,10*S**)-8-aza-tricyclo[8.1.2.0^{2,8}]-5-tridecen-9-one (**2-141c**) and
 (1*S**,2*R**,5*R**,8*S**)-5-vinyl-6-azatricyclo[6.1.2.0^{2,6}]undecan-7-one (**2-141b**). According to the general procedure VI, azides **2-140a**, **2-140b**, **2-140c**, and **2-140d** (98 mg, 0.45 mmol) and titanium tetrachloride (0.67 mL, 1 M in dichloromethane, 0.67 mmol) afforded lactam **2-141a** (53 mg, 62%) as a colorless oil, a mixture of lactams **2-141b** and **2-141c** (5 mg, 6%, 1:7 ratio) as a colorless oil, and a mixture of alcohols **2-141d**, **2-141e**, and **2-141f** (5 mg, 4%, 4.3:0.3:1 ratio) as a colorless oil after column chromatography (2-30% EtOAc/hexanes). Lactam **2-141a**: R_f = 0.2 (100% EtOAc/hexanes); IR (neat) 2946, 1649, 1415 cm⁻¹; HRMS (ESI) m/z calculated for C₁₂H₁₇NONa (M+Na)⁺ 214.1208, found: 214.1204; ¹H NMR (500 MHz, CDCl₃) δ 1.41-1.47 (m, 1H), 1.48-1.59 (m, 2H), 1.62 (d, J = 11.5 Hz, 1H), 1.69-1.82 (m, 4H), 1.91-1.99 (m, 1H), 2.01-2.11 (m, 1H), 2.37 (br, 1H), 2.70 (t, J = 4.0 Hz, 1H), 3.11 (td, J

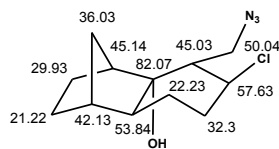
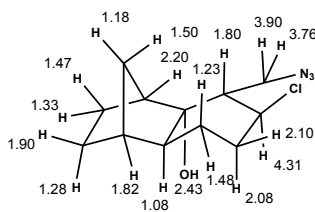
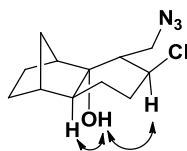
=2.0, 12.0 Hz, 1H), 4.19 (t, J = 8.5 Hz, 1H), 5.05 (td, J = 0.8, 10.0 Hz, 1H), 5.13 (td, J = 0.8, 17.0 Hz, 1H), 5.73-5.80 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 27.2 (CH_2), 29.5 (CH_2), 30.1 (CH_2), 31.6 (CH_2), 33.2 (CH_2), 36.5 (CH), 43.8 (CH), 57.8 (CH), 66.2 (CH), 114.3 (CH_2), 138.9 (CH), 175.6 (C). Mixture of lactams **2-141b** and **2-141c**: R_f = 0.25 (100% EtOAc/hexanes); IR (neat) 2941, 1639, 1450 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{17}\text{NONa}$ ($\text{M}+\text{Na}$) $^+$ 214.1208, found: 214.1218. Lactam **2-141c**: ^1H NMR (500 MHz, CDCl_3) δ 1.38-1.43 (m, 1H), 1.49-1.59 (m, 2H), 1.65-1.78 (m, 2H), 1.82-1.92 (m, 2H), 1.98 (d, J = 11.5 Hz, 1H), 2.19 (t, J = 6.0 Hz, 1H), 2.23-2.26 (m, 2H), 2.65 (t, J = 5.0 Hz, 1H), 3.00-3.04 (m, 1H), 3.18 (d, J = 9.5 Hz, 1H), 4.60 (dd, J = 7.0, 15.0 Hz, 1H), 5.84-5.89 (m, 1H), 5.90-5.95 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 26.4 (CH_2), 29.3 (CH_2), 29.7 (CH_2), 30.8 (CH_2), 34.5 (CH_2), 40.6 (CH), 43.7 (CH_2), 43.8 (CH), 69.5 (CH), 129.8 (CH), 134.0 (CH), 175.3 (C). Lactam **2-141b** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 2.10 (dtd, J = 1.0, 8.5, 13.0 Hz, 1H), 2.36 (t, J = 4.5 Hz, 1H), 2.68-2.71 (m, 1H), 3.13 (dd, J = 4.5, 11.5 Hz, 1H), 4.55-4.60 (m, 1H), 4.95 (td, J = 1.5, 10.5 Hz, 1H), 4.99 (td, J = 1.5, 17.0 Hz, 1H), 5.72 (ddd, J = 5.0, 10.5, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 28.4 (CH_2), 29.19 (CH_2), 29.24 (CH_2), 30.7 (CH_2), 31.8 (CH_2), 36.2 (CH), 43.5 (CH), 56.3 (CH), 64.8 (CH), 112.8 (CH_2), 138.7 (CH), 175.0 (C). The following data and NOE correlations were used to assign lactam **2-141a**, **2-141b** and **2-141c**.

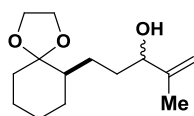




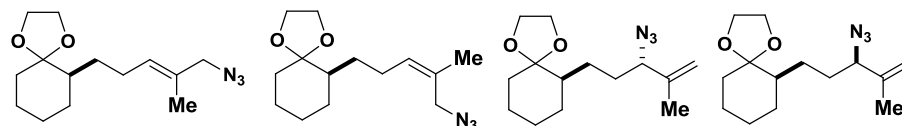
(1*R**,4*S**,4*aS**,5*S**,6*S**,8*aS**)-5-(Azidomethyl)-6-chlorodecahydro-1,4-methanonaphthalen-4a-ol (2-141d), (1*R**,4*S**,4*aS**,5*S**,6*R**,8*aS**)-5-(azidomethyl)-6-chlorodecahydro-1,4-methanonaphthalen-4a-ol (2-141e), and (1*R**,4*S**,4*aS**,5*S**,8*aS**)-5-(azidomethyl)-1,2,3,4,4*a*,5,8,8*a*-octahydro-1,4-methanonaphthalen-4a-ol (2-141f).

Alcohol **2-141d**, **2-141e**, and **2-141f**: R_f = 0.25 (10% EtOAc/hexanes); IR (neat) 3502, 2945, 2101 cm^{-1} . Alcohol **2-141d**: ^1H NMR (500 MHz, CDCl_3) δ 1.09 (ddd, J = 2.3, 6.5, 12.5 Hz, 1H), 1.17-1.26 (m, 2H), 1.27-1.32 (m, 1H), 1.33-1.40 (m, 1H), 1.47-1.55 (m, 3H), 1.81-1.86 (m, 2H), 1.87-1.95 (m, 1H), 2.06-2.15 (m, 2H), 2.17-2.23 (m, 1H), 2.43 (s, 1H), 3.76 (dd, J = 3.0, 13.0 Hz, 1H), 3.89 (dd, J = 3.8, 13.0 Hz, 1H), 4.31 (ddd, J = 2.0, 7.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.2 (CH_2), 22.2 (CH_2), 29.9 (CH_2), 32.3 (CH_2), 36.0 (CH_2), 42.1 (CH), 45.0 (CH), 45.1 (CH), 50.0 (CH_2), 53.8 (CH), 57.6 (CH), 82.1 (C). Alcohol **2-141e** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 3.17 (dd, J = 3.8, 12.5 Hz, 1H), 3.53 (dd, J = 4.0, 12.5 Hz, 1H), 4.47 (ddd, J = 3.5, 7.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 79.3 (C). Alcohol **2-141f** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 1.13 (ddd, J = 2.3, 7.0, 11.0 Hz, 1H), 2.29 (d, J = 3.2 Hz, 1H), 3.39 (dd, J = 9.0, 12.5 Hz, 1H), 3.60 (dd, J = 4.0, 12.5 Hz, 1H), 5.68 (td, J = 3.0, 9.0 Hz, 1H), 5.96-6.01 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 22.4 (CH_2), 27.9 (CH_2), 29.3 (CH_2), 36.7 (CH_2), 42.0 (CH), 43.5 (CH), 45.4 (CH), 52.5 (CH_2), 56.0 (CH), 84.1 (C), 129.1 (CH), 130.1 (CH). The following data and NOE correlations were used to assign lactam **2-141d**.



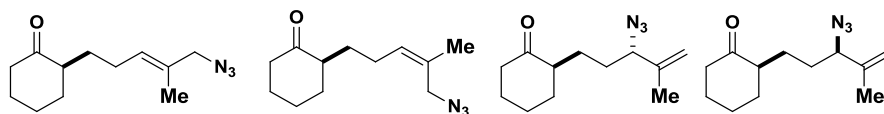


6-(3-Hydroxy-4-methylpent-4-enyl)-1,4-dioxaspiro(4.5)decane. To a stirred solution of isopropenylmagnesium bromide (40 mL, 0.5 M in THF, 20.0 mmol) in THF (20 mL) at -78 °C under N₂ atmosphere was added slowly a solution of **2-88** (2.0 g, 10.1 mmol) in anhydrous THF (5 mL). After stirring overnight and warmed to rt, saturated NH₄Cl was added. The aqueous layer was washed three times with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄. The concentrated residue was purified by chromatography (6-25% EtOAc/hexanes) to afford 6-(3-hydroxy-4-methylpent-4-enyl)-1,4-dioxaspiro(4.5)decane (1.6 g, 66%, 1:1 ratio) as a colorless oil. *R_f* = 0.45 (50% EtOAc/hexanes); IR (neat): 3436, 2932 cm⁻¹; HRMS (ESI) *m/z* calculated for C₂₈H₄₈O₆Na (2M+Na)⁺ 503.3349, found: 503.3332; ¹H NMR (400 MHz, CDCl₃, both isomers) δ 1.10-1.40 (m, 4H), 1.43-1.53 (m, 2H), 1.57-1.70 (m, 4H), 1.72 (s, 3H), 1.73-1.95 (m, 3H), 3.90-3.98 (m, 4H), 4.00-4.05 (m, 1H), 4.81-4.83 (m, 1H), 4.91-4.95 (m, 1H); ¹³C NMR (100 MHz, CDCl₃, both isomers) δ 17.3 (CH₃), 17.8 (CH₃), 23.8 (CH₂), 24.2 (CH₂), 24.3 (CH₂), 24.5 (CH₂), 29.2 (CH₂), 29.3 (CH₂), 33.0 (CH₂), 33.1 (CH₂), 34.6 (CH₂), 44.3 (CH), 44.6 (CH), 64.6 (CH₂), 64.7 (CH₂), 75.8 (CH), 76.6 (CH), 110.6 (CH₂), 110.87 (C), 110.90 (C), 111.2 (CH₂), 147.5 (C), 147.8 (C).



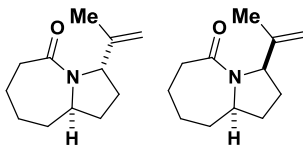
(*R*^{*},*E*)-6-(5-Azido-4-methylpent-3-enyl)-1,4-dioxaspiro(4.5)decane (2-180a),
(*R*^{*},*Z*)-6-(5-azido-4-methylpent-3-enyl)-1,4-dioxaspiro(4.5)decane (2-180b), (*R*^{*})-6-((*S*^{*})-

3-azido-4-methylpent-4-enyl)-1,4-dioxaspiro(4.5)decane (2-180c), and (*R)-6-((*R**)-3-azido-4-methylpent-4-enyl)-1,4-dioxaspiro(4.5)decane (2-180d)** According to the procedure described for the synthesis of azides **85** (Method A), the reaction of 6-(3-hydroxy-4-methylpent-4-enyl)-1,4-dioxaspiro(4.5)decane (1.12 g, 5.0 mmol), PPh₃ (2.62 g, 10.0 mmol), Zn(N₃)₂·2Pyr (1.53 g, 5.0 mmol), and DEAD (4.35 g, 40% in toluene, 10.0 mmol) in benzene (40 mL) afforded a mixture of azides **2-180a**, **2-180b**, **2-180c**, and **2-180d** (1.12 g, 85%, ratio: 38:12:25:25 from ¹H NMR in CDCl₃) as a colorless oil after column chromatography (0.5-3% EtOAc/hexanes). Azides **2-180a**, **2-180b**, **2-180c**, and **2-180d**: *R_f* = 0.45 (10% EtOAc/hexanes); IR (neat): 2934, 2094 cm⁻¹; HRMS (ESI) *m/z* calculated for C₂₈H₄₆N₆O₄Na (2M+Na)⁺ 553.3478, found: 553.3474. Azide **2-180a**: ¹H NMR (400 MHz, CDCl₃) δ 1.10-2.20 (m, 13H), 3.67 (s, 2H), 3.90-4.00 (m, 4H), 5.44 (dt, *J* = 1.0 Hz, 7.2 Hz, 1H). Azide **2-180b** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 3.78 (s, 2H). Azides **2-180c** and **2-180d** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 3.79-3.84 (m, 1H), 4.96 (s, 1H), 4.98 (dt, *J* = 1.6 Hz, 4.8 Hz, 1H). Azides **2-180a**, **2-180b**, **2-180c**, and **2-180d**: ¹³C NMR (100 MHz, CDCl₃) δ 14.6 (CH₃), 17.5 (CH₃), 17.8 (CH₃), 22.3 (CH₃), 23.8 (CH₂), 23.9 (CH₂), 24.49 (CH₂), 24.52 (CH₂), 24.9 (CH₂), 25.0 (CH₂), 25.7 (CH₂), 25.9 (CH₂), 27.8 (CH₂), 28.6 (CH₂), 29.0 (CH₂), 29.1 (CH₂), 29.23 (CH₂), 29.27 (CH₂), 30.4 (CH₂), 30.7 (CH₂), 34.6 (CH₂), 34.7 (CH₂), 44.1 (CH), 44.4 (CH), 44.5 (CH), 51.2 (CH₂), 59.5 (CH₂), 64.62 (CH₂), 64.64 (CH₂), 64.68 (CH₂), 64.74 (CH₂), 64.76 (CH₂), 64.77 (CH₂), 69.0 (CH), 69.1 (CH), 110.66 (C), 110.69 (C), 110.79 (C), 110.83 (C), 114.2 (CH₂), 114.7 (CH₂), 128.8 (C), 129.4 (C), 131.1 (CH), 131.7 (CH), 142.2 (C), 142.6 (C).



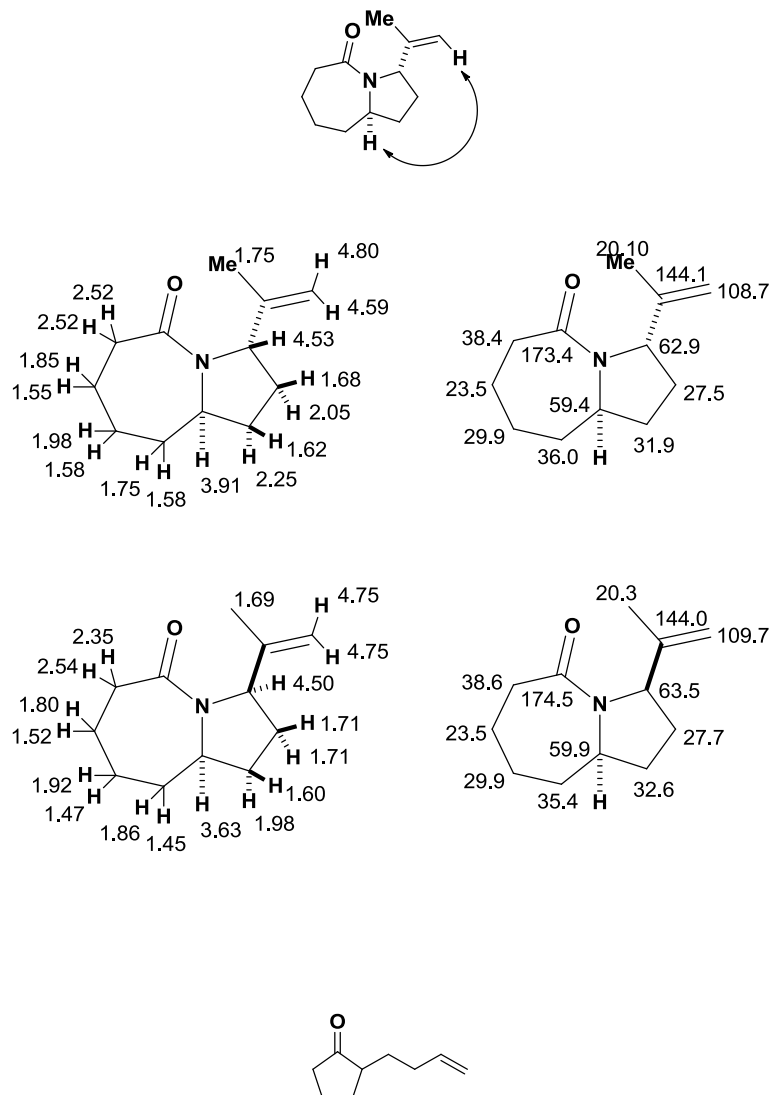
(*R*^{*},*E*)-2-(5-Azido-4-methylpent-3-enyl)cyclohexanone (2-178a), (*R*^{*},*Z*)-2-(5-azido-4-methylpent-3-enyl)cyclohexanone (2-178b), (*R*^{*})-2-((*S*^{*})-3-azido-4-methylpent-4-enyl)cyclohexanone (2-178c), and (*R*^{*})-2-((*R*^{*})-3-azido-4-methylpent-4-enyl)cyclohexanone (2-178d). According to the first procedure described for azide **91a** and **91b**, the reaction of ketal **2-180a**, **2-180b**, **2-180c**, and **2-180d** (724 mg, 2.73 mmol) and I₂ (70 mg, 0.27 mmol) in acetone (20 mL) afforded a mixture of azide **2-178a**, **2-178b**, **2-178c**, and **2-178d** (500 mg, 83%, ratio: 40:8:26:26 from ¹H NMR in CDCl₃) as a colorless oil after chromatography (0.6-2% EtOAc/hexanes). Azide **2-178a**, **2-178b**, **2-178c**, and **2-178d**: *R_f* = 0.55 (10% EtOAc/hexanes); IR (neat): 2935, 2095, 1710, 1449, 1243 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₂H₁₉N₃ONa (M+Na)⁺ 244.1426, found: 244.1439. Azide **2-178a**: ¹H NMR (400 MHz, CDCl₃) δ 1.18-1.31 (m, 1H), 1.36-1.45 (m, 1H), 1.48-1.63 (m, 1H), 1.64-1.78 (m, 2H), 1.71 (s, 3H), 1.80-1.93 (m, 2H), 2.04-2.15 (m, 3H), 2.26-2.36 (m, 2H), 2.38-2.43 (m, 1H), 3.67 (s, 2H), 5.41-5.42 (dt, *J* = 1.2 Hz, 7.2 Hz, 1H). Azide **2-178b** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 1.61 (s, 3H), 3.79 (d, *J* = 6.8 Hz, 2H), 5.47 (t, *J* = 7.6 Hz, 1H). Azides **2-178c** and **2-178d** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 1.74-1.76 (m, 3H), 3.85 (q, *J* = 7.2 Hz, 1H), 4.98 (s, 1H), 5.00 (quintet, *J* = 1.6 Hz, 1H). Azides **2-178a**, **2-178b**, **2-178c**, and **2-178d**: ¹³C NMR (100 MHz, CDCl₃, all isomers) δ 14.6 (CH₃), 17.6 (CH₃), 20.9 (CH₃), 22.3 (CH₃), 25.0 (CH₂), 25.1 (CH₂), 25.4 (CH₂), 25.6 (CH₂), 25.8 (CH₂), 25.9 (CH₂), 26.4 (CH₂), 27.8 (CH₂), 28.05 (CH₂), 28.08 (CH₂), 29.1 (CH₂), 29.5 (CH₂), 29.7 (CH₂), 29.8 (CH₂), 30.2 (CH₂), 33.9 (CH₂), 34.09 (CH₂), 34.15 (CH₂), 38.3 (CH₂), 39.3 (CH₂), 42.13 (CH₂), 42.17 (CH₂), 42.9 (CH₂), 49.0 (CH₂), 49.9 (CH), 50.2 (CH), 50.5 (CH), 51.1 (CH₂), 59.4 (CH₂), 68.6 (CH), 68.9 (CH), 114.7 (CH₂), 114.8 (CH₂), 129.6 (C), 130.1

(C), 130.2 (CH₂), 130.9 (CH₂), 142.0 (C), 142.2 (C), 212.7 (C), 212.8 (C), 213.1 (C), 213.2 (C).



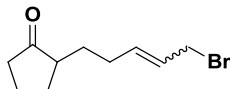
(3S*,9aR*)-3-(Prop-1-en-2-yl)-hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (2-179a) and **(3R*, 9aR*)-3-(prop-1-en-2-yl)-hexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (2-179b)** According to the general procedure VI, the reaction of azide **2-178a**, **2-178b**, **2-178c** and **2-178d** (108 mg, 0.49 mmol) and tin chloride (0.73 mL, 1 M in dichloromethane, 0.73 mmol) in anhydrous dichloromethane (17 mL) afforded lactam **2-179a** (20 mg, 21%) as a colorless oil and lactam **2-179b** (4 mg, 4%) as a colorless oil after column chromatography (12-35% EtOAc/hexanes). Lactam **2-179a**: R_f = 0.45 (100% EtOAc/hexanes); IR (neat): 2924, 1639, 1447, 1413 cm⁻¹; HRMS (ESI) m/z calculated for C₁₂H₂₀NO (M+H)⁺ 194.1545, found: 194.1550; ¹H NMR (400 MHz, CDCl₃) δ 1.52-1.81 (m, 6H), 1.75 (s, 3H), 1.83-1.90 (m, 1H), 1.97-2.08 (m, 2H), 2.21-2.31 (m, 1H), 2.48-2.54 (m, 2H), 3.91 (t, J = 9.2 Hz, 1H), 4.53 (d, J = 8.2 Hz, 1H), 4.59 (s, 1H), 4.80 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.1 (CH₃), 23.5 (CH₂), 27.5 (CH₂), 29.9 (CH₂), 31.9 (CH₂), 36.0 (CH₂), 38.4 (CH₂), 59.4 (CH), 62.9 (CH), 108.7 (CH₂), 144.1 (C), 173.4 (C). Lactam **2-179b**: R_f = 0.40 (100% EtOAc/hexanes); IR (neat): 2924, 1639, 1412 cm⁻¹; HRMS (ESI) m/z calculated for C₁₂H₂₀NO (M+H)⁺ 194.1545, found: 194.1546; ¹H NMR (500 MHz, CDCl₃) δ 1.42-1.55 (m, 3H), 1.57-1.65 (m, 1H), 1.68-1.75 (m, 2H), 1.69 (s, 3H), 1.79-1.88 (m, 2H), 1.89-1.95 (m, 1H), 1.96-2.03 (m, 1H), 2.31-2.38 (m, 1H), 2.54 (dd, J = 8.0 Hz, 15.0 Hz, 1H), 3.63 (dd, J = 9.2 Hz, 16.5 Hz, 1H), 4.48-4.52 (m, 1H), 4.75-4.77 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 20.3 (CH₃), 23.5 (CH₂), 27.8 (CH₂), 29.9 (CH₂), 32.6 (CH₂), 35.4 (CH₂), 38.6 (CH₂), 59.9 (CH), 63.5 (CH), 109.8 (CH₂),

144.0 (C), 174.5 (C). The following data and NOE correlations were used to assign lactams **2-179a** and **2-179b**.

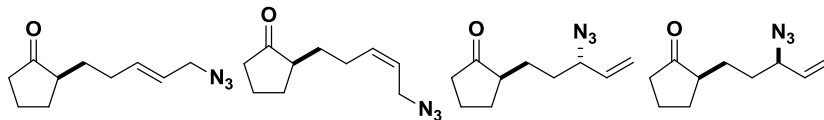


2-(But-3-en-1-yl)cyclopentanone.¹¹² According to the general procedure **V**, 2-cyclopentylidene-1,1-dimethylhydrazine (3.16 g, 25.0 mmol) and 4-bromo-1-butene (4.46 g, 33.0 mmol) afforded 2-(but-3-en-1-yl)cyclopentanone (colorless oil, 1.38 g, 40%) as a colorless oil after column chromatography (2-5% EtOAc/hexanes). R_f = 0.70 (20% EtOAc/hexanes); IR (neat): 2962, 1736 cm⁻¹; HRMS (EI) m/z calculated for C₉H₁₄O (M⁺)

138.1045, found: 138.1058; ^1H NMR (400 MHz, CDCl_3) δ 1.31-1.38 (m, 1H), 1.49-1.56 (m, 1H), 1.75-1.81 (m, 1H), 1.86-1.92 (m, 1H), 1.98-2.32 (m, 7H), 4.95-5.05 (m, 2H), 5.74-5.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.7 (CH_2), 28.8 (CH_2), 29.6 (CH_2), 31.6 (CH_2), 38.1 (CH_2), 48.4 (CH), 115.0 (CH_2), 138.0 (CH), 221.3 (C).

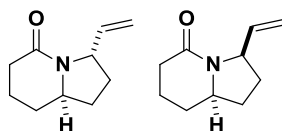


2-(5-Bromopent-3-en-1-yl)cyclopentanone. According to the general procedure **I**, 2-(but-3-en-1-yl)cyclopentanone (1.30 g, 9.4 mmol), HG-2 (118 mg, 0.19 mmol, 2 mol%) and allyl boromide (1.6 mL, 18.8 mmol) afforded 2-(5-bromopent-3-en-1-yl)cyclopentanone (colorless oil, 900 mg, 42%, *E/Z*: 6:1 ratio) as a colorless oil after column chromatography (2% EtOAc/hexanes). R_f = 0.55 (20% EtOAc/hexanes); IR (neat): 2961, 1736, 1205, 1155 cm^{-1} . Trans isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.32-1.41 (m, 1H), 1.45-1.56 (m, 1H), 1.76-1.92 (m, 2H), 2.01-2.33 (m, 7H), 3.93 (d, J = 6.4 Hz, 2H), 5.71-5.75 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 20.7 (CH_2), 28.8 (CH_2), 29.5 (CH_2), 29.9 (CH_2), 33.2 (CH_2), 38.1 (CH_2), 48.4 (CH), 127.1 (CH), 135.5 (CH), 221.05 (C). Cis isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.99 (d, J = 8.4 Hz, 2H), 5.55-5.61 (m, 1H), 5.71-5.75 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.9 (CH_2), 27.1 (CH_2), 29.1 (CH_2), 29.7 (CH_2), 126.1 (CH), 134.9 (CH), 221.01 (C).



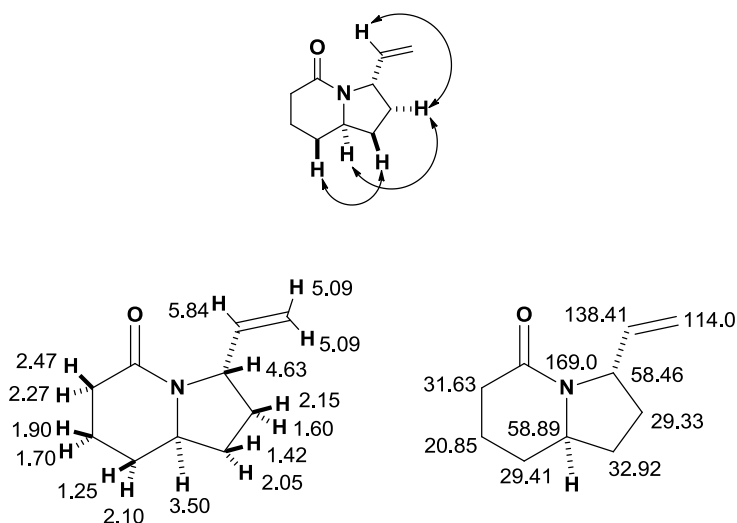
(*R,*E*)-2-(5-Azidopent-3-en-1-yl)cyclopentanone (2-148a), (*R**,*Z*)-2-(5-azidopent-3-en-1-yl)cyclopentanone (2-148b), (*R**)-2-((*S**)-3-azidopent-4-en-1-yl)cyclopentanone (2-148c), and (*R**)-2-((*R**)-3-azidopent-4-en-1-yl)cyclopentanone (2-148d).** According to

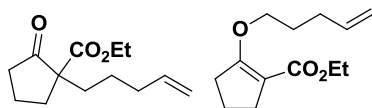
the general procedure **II**, 2-(5-bromopent-3-en-1-yl)cyclopentanone (900 mg, 3.9 mmol) and sodium azide (760 mg, 11.7 mmol) afforded a mixture of azides **2-148a**, **2-148b**, **2-148c**, and **2-148d** (colorless oil, 590 mg, 80%, 67:7:13:13 from ^1H NMR in acetone; 66:8:13:13 from ^1H NMR in CDCl_3) after column chromatography (1-6% EtOAc/hexanes). Azides **2-148**, **2-148b**, **2-148c**, and **2-148d**: R_f = 0.45 (20% EtOAc/hexanes); IR (neat): 2962, 2098, 1738 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{30}\text{N}_6\text{O}_2\text{Na}$ ($2\text{M}+\text{Na}$) $^+$ 409.2328, found: 409.2321. Azide **2-148a**: ^1H NMR (400 MHz, acetone) δ 1.30-1.40 (m, 1H), 1.52-1.61 (m, 1H), 1.72-1.87 (m, 2H), 1.96-2.25 (m, 7H), 3.78 (d, J = 6.4 Hz, 2H), 5.54-5.66 (m, 1H), 5.75-5.87 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.7 (CH_2), 29.0 (CH_2), 29.7 (CH_2), 30.1 (CH_2), 38.1 (CH_2), 48.3 (CH), 52.7 (CH_2), 123.7 (CH), 136.0 (CH), 221.0 (C). Azide **2-148b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.92 (d, J = 7.2 Hz, 2H). Azides **2-148c** and **2-148d** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 4.00 (q, J = 7.2 Hz, 1H), 5.28-5.37 (m, 2H), 5.75-5.87 (m, 1H). Azides **2-148b**, **2-148c**, and **2-148d** (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 65.01 (CH), 65.06 (CH), 118.38 (CH_2), 118.46 (CH_2), 122.92 (CH), 135.20 (CH), 135.41 (CH), 135.50 (CH), 220.6 (C), 220.9 (C).



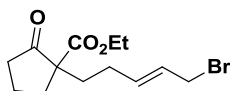
(3S*,8aR*)-3-Vinylhexahydroindolizin-5(1H)-one (2-149a) and (3R*,8aR*)-3-vinylhexahydroindolizin-5(1H)-one (2-149b). According to the general procedure **VI**, azides **2-148**, **2-148b**, **2-148c**, and **2-148d** (101 mg, 0.52 mmol) and tin tetrachloride (1.57 mL, 1 M in dichloromethane, 1.57 mmol) at room temperature afforded lactam **2-149a** (colorless oil, 21 mg, 24%) as a colorless oil and lactam **2-149b** (colorless oil, 12.5 mg, 15%) after column chromatography (3-100% EtOAc/hexanes). Lactam **2-149a**: R_f = 0.35 (100%

EtOAc); IR (neat): 2944, 1635, 1412 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{16}\text{NO}$ ($\text{M}+\text{H}$) $^{+}$ 166.1232, found: 166.1212; ^1H NMR (400 MHz, CDCl_3) δ 1.21-1.31 (m, 1H), 1.36-1.47 (m, 1H), 1.55-1.65 (m, 1H), 1.65-1.75 (m, 1H), 1.89-1.93 (m, 1H), 2.04-2.18 (m, 3H), 2.22-2.31 (m, 1H), 2.47 (dd, $J = 6.0$ Hz, 18.0 Hz, 1H), 3.50 (septet, $J = 4.8$ Hz, 1H), 4.64 (q, $J = 6.8$ Hz, 1H), 5.07-5.16 (m, 2H), 5.79-5.88 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.9 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.6 (CH_2), 32.9 (CH_2), 58.5 (CH), 58.9 (CH), 114.0 (CH_2), 138.4 (CH), 169.0 (C). Lactam **2-149b**: $R_f = 0.30$ (100% EtOAc); IR (neat): 2943, 1634, 1447 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{16}\text{NO}$ ($\text{M}+\text{H}$) $^{+}$ 166.1232, found: 166.1218; ^1H NMR (400 MHz, CDCl_3) δ 1.35-1.46 (m, 1H), 1.58-1.65 (m, 1H), 1.71-1.81 (m, 3H), 1.92-2.03 (m, 3H), 2.06-2.12 (m, 1H), 2.30-2.42 (m, 1H), 3.46 (tdd, $J = 3.2$ Hz, 4.4 Hz, 11.2 Hz, 1H), 4.58 (t, $J = 6.8$ Hz, 1H), 5.03-5.11 (m, 2H), 5.77-5.85 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.2 (CH_2), 29.0 (CH_2), 29.7 (CH_2), 30.5 (CH_2), 31.2 (CH_2), 58.1 (CH), 60.1 (CH), 114.0 (CH_2), 137.9 (CH), 169.4 (C). The following data and NOE correlations were used to assign lactam **2-149a**.

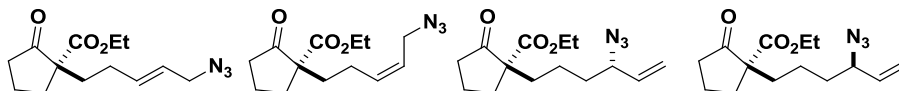




Ethyl 2-oxo-1-(pent-4-en-1-yl)cyclopentanecarboxylate and ethyl 2-(pent-4-en-1-yloxy)cyclopent-1-enecarboxylate. A suspension of ethyl 2-oxocyclopentanecarboxylate (15.62 g, 0.1 mol), 5-bromo-1-pentene (14.9 g, 0.1 mol) and potassium carbonate (27.6 g, 0.2 mol) in acetone (120 mL) under N₂ atmosphere was refluxed for about 36 h. After cooling down to room temperature, the reaction mixture was filtrated and the filtrate was concentrated. The residue was purified by chromatography (5-20% EtOAc/hexanes) to afford ethyl 2-oxo-1-(pent-4-en-1-yl)cyclopentanecarboxylate (colorless oil, 19.3 g, 86%) and ethyl 2-(pent-4-en-1-yloxy)cyclopent-1-enecarboxylate (colorless oil, 2.1 g, 9%). Ethyl 2-oxo-1-(pent-4-en-1-yl)cyclopentanecarboxylate: R_f = 0.45 (20% EtOAc/hexanes); IR (neat): 2978, 1750, 1723 cm⁻¹; HRMS (ESI) m/z calculated for C₁₃H₂₁O₃ (M+H)⁺ 225.1491, found: 225.1475; ¹H NMR (400 MHz, CDCl₃) δ 1.24 (t, J = 7.2 Hz, 3H), 1.26-1.34 (m, 1H), 1.46-1.48 (m, 1H), 1.56 (dt, J = 4.4 Hz, 12.4 Hz 1H), 1.88-2.07 (m, 6H), 2.20-2.29 (m, 1H), 2.36-2.41 (m, 1H), 2.49-2.54 (m, 1H), 4.15 (dq, J = 2.4 Hz, 7.2 Hz, 2H), 4.94-5.02 (m, 2H), 5.73-5.80 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.1 (CH₃), 19.6 (CH₂), 24.1 (CH₂), 32.8 (CH₂), 33.3 (CH₂), 33.9 (CH₂), 37.9 (CH₂), 60.4 (C), 61.3 (CH₂), 114.9 (CH₂), 138.1 (CH), 171.0 (C), 214.9 (C). Ethyl 2-(pent-4-en-1-yloxy)cyclopent-1-enecarboxylate: R_f = 0.40 (20% EtOAc/hexanes); IR (neat): 2977, 1683, 1227, 1057 cm⁻¹; HRMS (ESI) m/z calculated for C₁₃H₂₀O₃Na (M+Na)⁺ 247.1310, found: 247.1299; ¹H NMR (400 MHz, CDCl₃) δ 1.25 (t, J = 7.2 Hz, 3H), 1.74-1.85 (m, 4H), 2.16-2.21 (m, 1H), 2.50-2.62 (m, 4H), 3.99 (t, J = 6.4 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 4.94-5.04 (m, 2H), 5.75-5.82 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.4 (CH₃), 19.3 (CH₂), 28.8 (CH₂), 29.2 (CH₂), 29.7 (CH₂), 31.6 (CH₂), 59.2 (CH₂), 69.6 (CH₂), 104.2 (C), 115.2 (CH₂), 137.6 (CH), 165.3 (C), 168.4 (C).

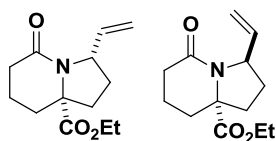


Ethyl 1-(5-bromopent-3-en-1-yl)-2-oxocyclopentanecarboxylate. To a refluxing suspension of ethyl 2-oxo-1-(pent-4-en-1-yl)cyclopentanecarboxylate (1.7 g, 7.6 mmol) and NBS (1.5 g, 8.4 mmol) in CCl_4 (50 mL) under N_2 atmosphere was added catalytic amount of benzoyl peroxide. After refluxing for 1.5 h, the solvent was removed in vacuo. The residue was purified by chromatography (4-20% EtOAc/hexanes) to afford ethyl 1-(5-bromopent-3-en-1-yl)-2-oxocyclopentanecarboxylate (colorless oil, 1.75 g, 76%). R_f = 0.45 (20% EtOAc/hexanes); IR (neat): 2974, 1749, 1723 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{19}\text{BrO}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 325.0415, found: 325.0389; ^1H NMR (400 MHz, CDCl_3) δ 1.24 (t, J = 7.2 Hz, 3H), 1.64-1.67 (m, 1H), 1.88-2.02 (m, 5H), 2.10-2.16 (m, 1H), 2.20-2.27 (m, 1H), 2.37-2.44 (m, 1H), 2.48-2.53 (m, 1H), 3.90 (d, J = 6.4 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 5.68-5.72 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (CH_3), 19.6 (CH_2), 27.5 (CH_2), 32.8 (CH_2), 32.9 (CH_2), 33.1 (CH_2), 37.9 (CH_2), 60.0 (C), 61.4 (CH_2), 127.0 (CH), 135.1 (CH), 170.8 (C), 214.6 (C).



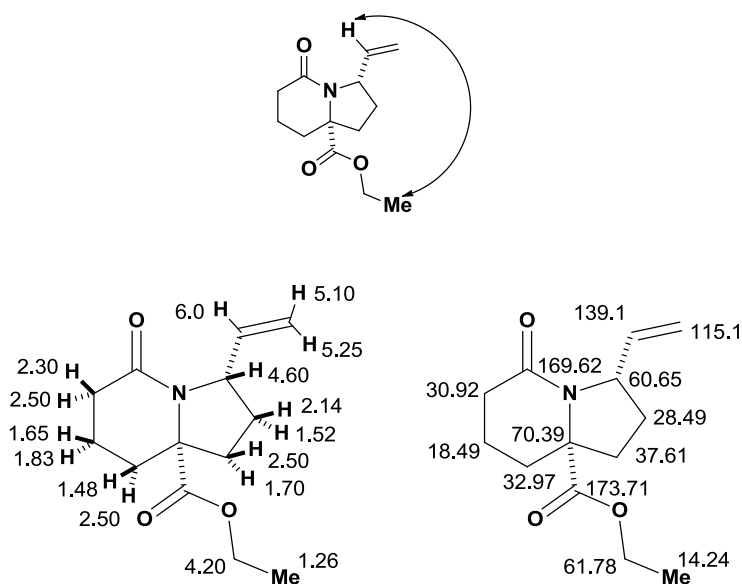
(S^* , E)-Ethyl 1-(5-azidopent-3-en-1-yl)-2-oxocyclopentanecarboxylate (2-150a), (S^* , Z)-ethyl 1-(5-azidopent-3-en-1-yl)-2-oxocyclopentanecarboxylate (2-150b), (R^*)-ethyl 1-((S^*)-4-azidohex-5-en-1-yl)-2-oxocyclopentanecarboxylate (2-150c), and (R^*)-ethyl 1-((R^*)-4-azidohex-5-en-1-yl)-2-oxocyclopentanecarboxylate (2-150d). According to the general procedure II, ethyl 1-(5-bromopent-3-en-1-yl)-2-oxocyclopentanecarboxylate (1.75 g, 5.75 mmol) and sodium azide (1.63 g, 25 mmol) afforded a mixture of azides **2-150a**,

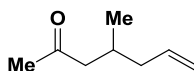
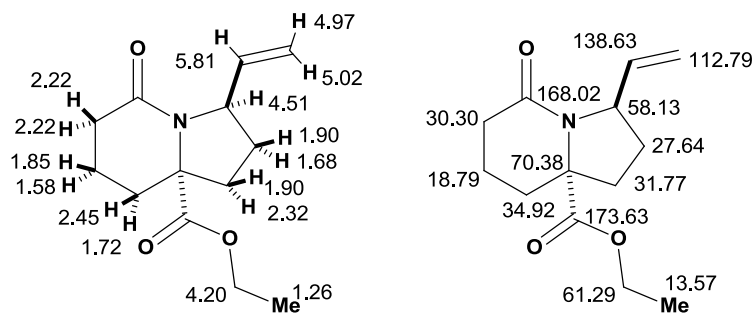
2-150b, **2-150c**, and **2-150d** (colorless oil, 900 mg, 59%, 61:9:15:15 from ^1H NMR in DMSO; 64:6:15:15 from ^1H NMR in CDCl_3) after column chromatography (2-10% EtOAc/hexanes). Azides **2-150a**, **2-150b**, **2-150c**, and **2-150d**: R_f = 0.65 (20% EtOAc/hexanes); IR (neat): 2977, 2098, 1750, 1723 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 288.1324, found: 288.1294. Azide **2-150a**: ^1H NMR (400 MHz, CDCl_3) δ 1.18 (t, J = 7.2 Hz, 3H), 1.53-1.64 (m, 1H), 1.78-2.00 (m, 5H), 2.07-2.21 (m, 2H), 2.31-2.48 (m, 2H), 3.63 (d, J = 6.4 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 5.44-5.49 (m, 1H), 5.61-5.69 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0 (CH_3), 19.5 (CH_2), 27.6 (CH_2), 32.9 (CH_2), 33.1 (CH_2), 37.8 (CH_2), 52.5 (CH_2), 60.0 (CH_2), 61.3 (CH_2), 123.6 (CH), 135.4 (CH), 170.7 (C), 214.4 (C). Azide **2-150b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.73-3.76 (m, 2H). Azide **2-150c** and **2-150d** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.73-3.76 (m, 1H), 5.20-5.24 (m, 2H), 5.61-5.69 (m, 1H). Azide **2-150b**, **2-150c**, and **2-150d** (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 64.87 (CH), 64.91 (CH), 118.49 (CH_2), 118.53 (CH_2), 122.9 (CH), 134.6 (CH), 135.1 (CH), 135.2 (CH), 170.76 (C), 170.79 (C), 214.37 (C).



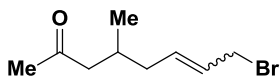
(3S*,8aR*)-Ethyl 5-oxo-3-Vinyloctahydroindolizine-8a-carboxylate (2-151a) and (3S*,8aR*)-ethyl 5-oxo-3-vinyloctahydroindolizine-8a-carboxylate (2-151b). According to the general procedure **VI**, azides **2-150a**, **2-150b**, **2-150c**, and **2-150d** (265 mg, 1 mmol) in TFA (2 mL) at room temperature afforded azides **2-150a**, **2-150b**, **2-150c**, and **2-150d** (72 mg, 27%), compound **2-151b** (35 mg, 15%) as a colorless oil and compound **2-151a** (10 mg, 4%) as a colorless oil after column chromatography (50-200% EtOAc/hexanes). Lactam **2-151a**: R_f = 0.45 (100% EtOAc); IR (neat): 2981, 1732, 1626 cm^{-1} ; HRMS (ESI) m/z calculated for

$C_{13}H_{20}O_3N$ ($M+H$)⁺ 238.1443, found: 238.1354; ¹H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 1.45-1.76 (m, 4H), 1.78-1.86 (m, 1H), 2.09-2.16 (m, 1H), 2.27-2.36 (m, 1H), 2.47-2.55 (m, 3H), 4.21 (dq, J = 2.8 Hz, 7.2 Hz, 2H), 4.61 (q, J = 7.6 Hz, 1H), 5.11-5.27 (m, 2H), 5.93-6.01 (m, 1H); ¹³C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 18.5 (CH_2), 28.5 (CH_2), 30.9 (CH_2), 33.0 (CH_2), 37.6 (CH_2), 60.6 (CH), 61.8 (CH_2), 70.4 (C), 115.1 (CH_2), 139.1 (CH), 169.6 (C), 173.7 (C). Lactam **2-151b**: R_f = 0.40 (100% EtOAc); IR (neat): 2938, 1732, 1655, 1400, 1185 cm^{-1} ; HRMS (ESI) m/z calculated for $C_{13}H_{20}O_3N$ ($M+H$)⁺ 238.1443, found: 238.1422; ¹H NMR (400 MHz, acetone) δ 1.26 (t, J = 7.2 Hz, 3H), 1.54-1.76 (m, 3H), 1.83-1.95 (m, 3H), 2.21-2.27 (m, 2H), 2.30-2.36 (m, 1H), 2.44 (dt, J = 4.0 Hz, 12.8 Hz, 1H), 4.21 (q, J = 7.2 Hz, 1H), 4.51 (t, J = 7.2 Hz, 1H), 4.95-5.04 (m, 2H), 5.77-5.86 (m, 1H); ¹³C NMR (100 MHz, acetone) δ 13.6 (CH_3), 18.8 (CH_2), 27.6 (CH_2), 30.3 (CH_2), 31.8 (CH_2), 34.9 (CH_2), 58.1 (CH), 61.3 (CH_2), 70.4 (C), 112.8 (CH_2), 138.6 (CH), 168.0 (C), 173.6 (C). The following data and NOE correlations were used to assign lactams **2-151a** and **2-151b**.

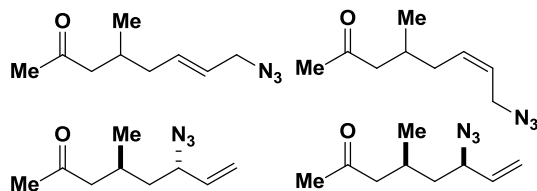




4-Methylhept-6-en-2-one.¹¹³ To a solution of (*E*)-pent-3-en-2-one (2.78 g, 33.1 mmol) in dichloromethane (75 mL) at -78 °C under N₂ atmosphere was added slowly titanium tetrachloride (1 M in dichloromethane, 35 mL, 35 mmol). After stirring for 30 min, allyltrimethylsilane (4.57 g, 40.0 mmol) was added to the resulting mixture over 20 min. After 4 h, the reaction was quenched by aqueous saturated ammonium chloride at 0 °C and extracted with diethyl ether. The combined organic extracts were washed with aqueous sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (2-10% EtOAc/hexanes) to afford 4-methylhept-6-en-2-one (colorless oil, 1.43 g, 11.3 mmol). *R*_f = 0.45 (10% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 0.90 (d, *J* = 6.4 Hz, 3H), 1.93-2.01 (m, 2H), 2.04-2.14 (m, 1H), 2.11 (s, 3H), 2.16-2.23 (m, 1H), 2.45 (dd, *J* = 2.8 Hz, 16 Hz, 1H), 4.97-5.02 (m, 2H), 5.68-5.78 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 19.7 (CH or CH₃), 28.9 (CH or CH₃), 30.4 (CH or CH₃), 41.1 (CH₂), 50.2 (CH₂), 116.4 (CH₂), 136.6 (CH), 208.7 (C).

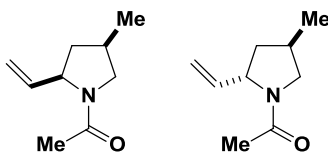


8-Bromo-4-methyloct-6-en-2-one. According to the general procedure **I**, 4-methylhept-6-en-2-one (1.43 g, 11.3 mmol), HG-2 (71 mg, 0.11 mmol, 1 mol%) and allyl bromide (2.9 mL, 34 mmol) afforded 8-bromo-4-methyloct-6-en-2-one (colorless oil, 1.48 g, 60%, *E/Z*: 5:1) after column chromatography (2-10% EtOAc/hexanes). *E* isomer: R_f = 0.30 (10% EtOAc/hexanes); IR (neat): 2958, 1714, 1205 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.92 (d, J = 6.4 Hz, 3H), 1.99-2.05 (m, 1H), 2.08-2.15 (m, 2H), 2.13 (s, 3H), 2.22-2.27 (m, 1H), 2.40-2.46 (m, 1H), 3.95 (d, J = 3.6 Hz, 2H), 5.66-5.77 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.7, 29.0, 30.5, 33.0, 39.1, 50.1, 128.4, 134.1, 208.3. *Z* isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 0.95 (d, J = 6.8 Hz, 3H), 3.99 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.8, 27.1, 29.1, 33.7, 50.2, 126.9, 133.3.



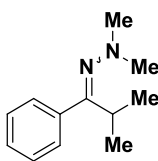
(*E*)-8-Azido-4-methyloct-6-en-2-one (2-172a), (*Z*)-8-azido-4-methyloct-6-en-2-one (2-172b), (*4S,*6S**)-6-azido-4-methyloct-7-en-2-one (2-172c), and (*4S**,*6R**)-6-azido-4-methyloct-7-en-2-one (2-172d).** According to the general procedure **II**, 8-bromo-4-methyloct-6-en-2-one (1.40 g, 6.38 mmol) and sodium azide (1.25 g, 19.2 mmol) afforded a mixture of azides **2-172a**, **2-172b**, **2-172c**, and **2-172d** (colorless oil, 865 mg, 75%, 79:11:5:5 from ^1H NMR in CDCl_3) after column chromatography (3-10% EtOAc/hexanes). Azides **2-172a**, **2-172b**, **2-172c**, and **2-172d**: R_f = 0.35 (10% EtOAc/hexanes); IR (neat): 2999, 2099, 1715 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{31}\text{N}_6\text{O}_2$ ($2\text{M}+\text{H}$) $^+$ 363.2508, found: 363.2509.

Azide **2-172a**: ^1H NMR (400 MHz, CDCl_3) δ 0.93 (d, $J = 6.4$ Hz, 3H), 1.99-2.14 (m, 3H), 2.13 (s, 3H), 2.25 (dd, $J = 7.6$ Hz, 16.4Hz, 1H), 2.45 (dd, $J = 5.6$ Hz, 16.4Hz, 1H), 3.71 (d, $J = 6.8$ Hz, 2H), 5.49-5.54 (m, 1H), 5.65-5.76 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.7 (CH or CH_3), 28.8 (CH or CH_3), 30.4 (CH or CH_3), 39.3 (CH_2), 50.1 (CH_2), 52.7 (CH_2), 125.0 (CH), 134.5 (CH), 208.3 (C). Azide **2-172b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.81 (d, $J = 7.2$ Hz, 2H). Azides **2-172c** and **2-172d** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.84-3.92 (m, 1H), 5.26-5.32 (m, 2H), 5.57-5.65 (m, 1H). Azides **2-172b**, **2-172c**, and **2-172d** (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 29.2 (CH or CH_3), 34.2 (CH_2), 47.2 (CH_2), 50.1 (CH_2), 118.0 (CH_2), 118.7 (CH_2), 123.9 (CH), 133.6 (CH).

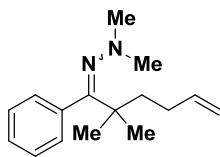


1-((2R*,4R*)-4-Methyl-2-vinylpyrrolidin-1-yl)ethanone (2-173a) and 1-((2S*,4R*)-4-methyl-2-vinylpyrrolidin-1-yl)ethanone (2-173b). According to the general procedure **VI**, azides **2-172a**, **2-172b**, **2-172c**, and **2-172d** (54 mg, 0.30 mmol) and tin tetrachloride (0.45 mL, 1 M in dichloromethane, 0.45 mmol) afforded a mixture of lactams **2-173a** and **2-173b** (colorless oil, 14 mg, 31%) by chromatography (5-100% EtOAc/hexanes). Lactams **2-173a** and **2-173b**: $R_f = 0.35$ (100% EtOAc); IR (neat): 2960, 1646, 1416 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_9\text{H}_{16}\text{NO}$ ($\text{M}+\text{H}$)⁺ 154.1232, found: 154.1229. Lactam **2-173a**: ^1H NMR (400 MHz, CDCl_3) δ 1.08 (d, $J = 6.8$ Hz, 3H), 1.40-1.47 (m, 1H), 2.01 (s, 3H), 2.10-2.21 (m, 1H), 2.34-2.43 (m, 1H), 2.83 (t, $J = 10.4$ Hz, 1H), 4.10 (ddd, $J = 0.8$ Hz, 6.8 Hz, 10.8Hz, 1H), 4.24 (q, $J = 7.6$ Hz, 1H), 5.13-5.18 (m, 2H), 5.73-5.83 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 17.5 (CH or CH_3), 22.3 (CH or CH_3), 31.7 (CH or CH_3), 42.6 (CH_2), 53.3

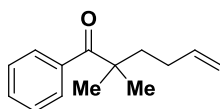
(CH₂), 61.6 (CH), 114.9 (CH₂), 140.0 (CH), 170.2 (C). Lactam **2-173b**: ¹H NMR (400 MHz, CDCl₃) δ 1.09 (d, *J* = 6.4 Hz, 3H), 1.34-1.43 (m, 1H), 2.08 (s, 3H), 2.21-2.33 (m, 2H), 3.04 (t, *J* = 6.0 Hz, 1H), 3.67 (ddd, *J* = 0.8 Hz, 8.0 Hz, 10.0 Hz, 1H), 4.49 (q, *J* = 7.2 Hz, 1H), 5.08-5.14 (m, 2H), 5.80-5.89 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 17.5 (CH or CH₃), 23.2 (CH or CH₃), 33.1 (CH or CH₃), 40.3 (CH₂), 55.4 (CH₂), 59.5 (CH), 113.9 (CH₂), 139.2 (CH), 169.0 (C).



1,1-Dimethyl-2-(2-methyl-1-phenylpropylidene)hydrazine.¹¹⁴ To a solution of isobutyrophenone (22.6 mL, 0.150 mol) and 1,1-dimethylhydrazine (34.2 mL, 0.450 mol) in 40 mL toluene was added p-toluenesulfonic acid monohydrate (0.29 g, 1.5 mmol). The reaction mixture was heated to reflux using a Dean-Stark apparatus for one day before the additional addition of 1,1-dimethylhydrazine (34 mL, 0.45 mol). The reaction mixture was allowed to reflux for 5 days. The reaction mixture was concentrated under reduced pressure and the residue was distilled under reduced pressure to afford 1,1-dimethyl-2-(2-methyl-1-phenylpropylidene)hydrazine (27.3 g, 100%, E/Z: 8:1) as a colorless oil. E isomer: ¹H NMR (400 MHz, CDCl₃) δ 1.10 (d, *J* = 6.8 Hz, 6H), 2.36 (s, 6H), 2.79 (septet, *J* = 6.8 Hz, 1H), 7.20-7.22 (m, 2H), 7.32-7.38 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 20.6 (CH₃), 37.1 (CH), 47.3 (CH₃), 127.1 (CH), 127.6 (CH), 128.0 (CH), 137.9 (C), 169.1 (C). Z isomer (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 1.16 (d, *J* = 6.8 Hz, 6H), 2.57 (s, 6H), 3.88 (septet, *J* = 6.8 Hz, 1H), 7.20-7.22 (m, 2H), 7.32-7.38 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 20.4 (CH₃), 29.1 (CH), 48.1 (CH₃), 132.8 (C), 175.8 (C).

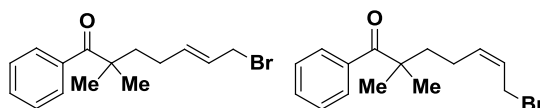


2-(2,2-Dimethyl-1-phenylhex-5-enylidene)-1,1-dimethylhydrazine. To a solution of 1,1-dimethyl-2-(2-methyl-1-phenylpropylidene)hydrazine (11.4 g, 60.0 mmol) in THF (100 mL) under N₂ atmosphere at 0 °C was added n-BuLi (30 mL, 2.5 M in hexane, 75 mmol). After stirring for 2 h, 4-bromo-1-butene (10.1 g, 75.0 mmol) was added dropwise at 0 °C. The reaction mixture was allowed naturally to warm to rt and stirred overnight. The reaction mixture was quenched with saturated NH₄Cl. After the separation, the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate. After the filtration and concentration, the residue was purified by chromatography (0.5-5% EtOAc/hexanes) to afford 2-(2,2-dimethyl-1-phenylhex-5-enylidene)-1,1-dimethylhydrazine (9.5 g, 65%) as a colorless oil. R_f = 0.40 (20% EtOAc/hexanes); IR (neat) 2965, 1640, 1467 cm⁻¹; HRMS (ESI) m/z calculated for (C₁₆H₂₄N₂+H)⁺ 245.2018, found: 245.2010; ¹H NMR (400 MHz, CDCl₃) δ 1.13 (s, 6H), 1.58-1.62 (m, 2H), 2.14-2.20 (m, 2H), 2.35 (s, 6H), 4.96-5.09 (m, 2H), 5.82-5.92 (m, 1H), 7.06-7.09 (m, 2H), 7.32-7.38 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 26.9 (CH₃), 29.3 (CH₂), 39.7 (CH₂), 41.4 (C), 47.4 (CH₃), 114.0 (CH₂), 127.2 (CH), 127.3 (CH), 127.8 (CH), 137.9 (C), 139.3 (CH), 170.7 (C).



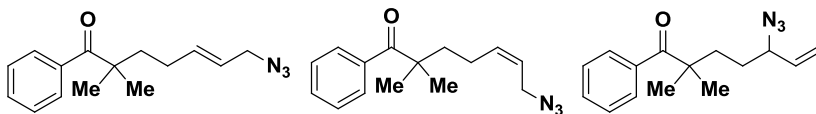
2,2-Dimethyl-1-phenylhex-5-en-1-one. A solution of 2-(2,2-dimethyl-1-phenylhex-5-enylidene)-1,1-dimethylhydrazine (3.9 g, 16 mmol) in a mixed solvent of CCl₄ (35 mL) and

2 M aqueous H₂SO₄ (35 mL) was heated to reflux for 10 h. After cooling to room temperature, the aqueous layer was separated from organic layer and washed twice with dichloromethane. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (0.5-1.5% EtOAc/hexanes) to afford 2,2-dimethyl-1-phenylhex-5-en-1-one (3.0 g, 93%) as a colorless oil. R_f = 0.50 (20% EtOAc/hexanes); IR (neat) 2973, 1674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.35 (s, 6H), 1.84-1.89 (m, 2H), 2.00-2.06 (m, 2H), 4.92-5.01 (m, 2H), 5.72-5.82 (m, 1H), 7.39-7.49 (m, 3H), 7.67-7.69 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 26.1 (2CH₃), 29.2 (CH₂), 40.1 (CH₂), 47.7 (C), 114.6 (CH₂), 127.5 (2CH), 128.1 (2CH), 130.8 (CH), 138.4 (CH), 139.1 (C), 209.0 (C).



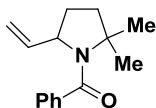
(*E*)-7-Bromo-2,2-dimethyl-1-phenylhept-5-en-1-one and (*Z*)-7-bromo-2,2-dimethyl-1-phenylhept-5-en-1-one. According to the general procedure I, 2,2-dimethyl-1-phenylhex-5-en-1-one (2.03 g, 10.0 mmol), HG-2 (125 mg, 0.20 mmol, 2 mol%) and allyl bromide (2.54 mL, 30.0 mmol) afforded a mixture of (*E*)-7-bromo-2,2-dimethyl-1-phenylhept-5-en-1-one and (*Z*)-7-bromo-2,2-dimethyl-1-phenylhept-5-en-1-one (2.44 g, 83%, 5:1 ratio) as a colorless oil after column chromatography (0.5-1.5% EtOAc/hexanes). R_f = 0.35 (5% EtOAc/hexanes); IR (neat) 2968, 1672, 1203, 965, 718, 699 cm⁻¹; HRMS (ESI) m/z calculated for (C₁₅H₁₉BrO+NH₄)⁺ 312.0963, found: 312.0968. *E* isomer: ¹H NMR (400 MHz, CDCl₃) δ 1.34 (s, 3H), 1.82-1.88 (m, 2H), 2.01-2.07 (m, 2H), 3.91 (d, J = 6.8 Hz, 1H), 5.61-5.78 (m, 2H), 7.39-7.48 (m, 3H), 7.66-7.73 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 26.1 (2CH₃), 27.6 (CH₂), 33.3 (CH₂), 39.9 (CH₂), 47.7 (C), 126.6 (CH), 127.6 (CH), 128.2 (CH),

131.0 (CH), 135.8 (CH), 138.9 (C), 208.6 (C). *Z* isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.37 (s, 3H), 3.85 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 125.8 (CH), 135.0 (CH), 208.9 (C).

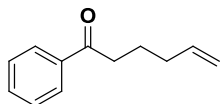


(*E*)-7-Azido-2,2-dimethyl-1-phenylhept-5-en-1-one (2-158a), (*Z*)-7-azido-2,2-dimethyl-1-phenylhept-5-en-1-one (2-158b), and 5-azido-2,2-dimethyl-1-phenylhept-6-en-1-one (2-158c). According to the general procedure II, (*E*)-7-bromo-2,2-dimethyl-1-phenylhept-5-en-1-one and (*Z*)-7-bromo-2,2-dimethyl-1-phenylhept-5-en-1-one (2.44 g, 8.30 mmol) and sodium azide (1.63 g, 25.0 mmol) afforded a mixture of azides **2-158a**, **2-158b** and **2-158c** (1.5 g, 71%, 53:11:36 ratio from ^1H NMR in CDCl_3) as colorless oil after column chromatography (0.25-1.5% EtOAc/hexanes). Azides **2-158a**, **2-158b** and **2-158c**: R_f = 0.45 (10% EtOAc/hexanes); IR (neat) 2968, 2094, 1671 cm^{-1} ; HRMS (ESI) m/z calculated for $(\text{C}_{30}\text{H}_{38}\text{N}_4\text{O}_2+\text{H})^+$ 487.3073 (corresponding to $(2\text{ M-N}_2+\text{H})^+$), found: 487.3087. Azide **2-158a**: ^1H NMR (400 MHz, CDCl_3) δ 1.34 (s, 3H), 1.82-1.89 (m, 2H), 2.01-2.08 (m, 2H), 3.67 (d, J = 6.8 Hz, 1H), 5.44-5.51 (m, 1H), 5.61-5.74 (m, 1H), 7.39-7.50 (m, 3H), 7.66-7.69 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.1 (2CH_3), 27.8 (CH_2), 40.4 (CH_2), 47.6 (C), 52.7 (CH_2), 123.1 (CH), 127.6 (CH), 128.2 (CH), 131.0 (CH), 136.3 (CH), 138.9 (C), 208.66 (C). Azide **2-158b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.36 (s, 3H), 3.64 (d, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.1 (CH_2), 26.2 (CH_3), 40.9 (CH_2), 47.0 (C), 52.1 (CH_2), 122.5 (CH), 127.7 (CH), 131.1 (CH), 135.3 (CH), 208.39 (C). Azide **2-158c** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.33 (s, 3H), 1.45-1.52 (m, 2H), 1.72-1.89 (m, 2H), 3.76 (q, J = 7.2 Hz, 1H), 5.22-5.27 (m, 2H), 5.61-5.74 (m, 1H); ^{13}C NMR (100

MHz, CDCl₃) δ 26.2 (CH₃), 29.7 (CH₂), 36.9 (CH₂), 47.4 (C), 65.3 (CH), 118.4 (CH₂), 127.6 (CH), 131.0 (CH), 135.4 (CH), 138.8 (C), 208.47 (C).

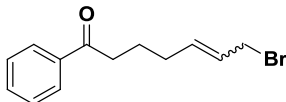


(2,2-Dimethyl-5-vinylpyrrolidin-1-yl)phenylmethanone (2-159). According to the procedure V, azides **2-158a**, **2-158b**, and **2-158c** (86 mg, 0.33 mmol) afforded after chromatography (1-8% EtOAc/hexanes) lactam **2-159** (41 mg, 54%) as a colorless oil. Lactam **2-159**: R_f = 0.20 (20% EtOAc/hexanes); IR (neat) 2965, 1627 cm⁻¹; HRMS (ESI) m/z calculated for (C₁₅H₁₉NO+Na)⁺ 252.1364, found: 252.1343; ¹H NMR (400 MHz, CDCl₃) δ 1.58 (br s, 3H), 1.58-1.70 (m, 1H), 1.70 (br s, 3H), 1.78-1.83 (m, 1H), 1.90-1.97 (m, 1H), 2.06-2.15 (m, 1H), 4.35 (br s, 3H), 4.76 (d, J = 16.4 Hz, 3H), 4.92 (d, J = 10.0 Hz, 3H), 5.58 (br s, 1H), 7.32 (s, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 25.4 (CH₃), 27.2 (CH₃), 29.3 (CH₂), 39.7 (CH₂), 63.0 (C), 63.5 (CH), 115.0 (CH₂), 126.2 (CH), 127.9 (CH), 128.7 (CH), 139.1 (CH), 170.7 (C).

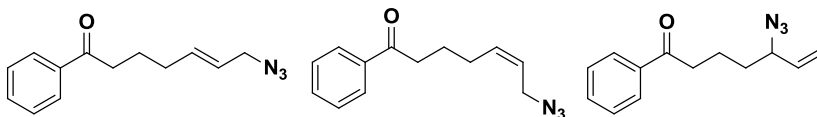


1-Phenylhex-5-en-1-one.¹¹³ According to the general procedure V, 1,1-dimethyl-2-(1-phenylethylidene)hydrazine (6.5 g, 40.0 mmol) and 4-bromo-1-butene (6.21 g, 46.0 mmol) afforded 1-phenylhex-5-en-1-one (colorless oil, 5.4 g, 78%) as a colorless oil after column chromatography (1-5% EtOAc/hexanes). R_f = 0.60 (10% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 1.84-1.91 (m, 2H), 2.18 (q, J = 7.2 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 5.00-5.09 (m, 2H), 5.79-5.89 (m, 1H), 7.45-7.49 (m, 2H), 7.54-7.58 (m, 1H), 7.96-7.98 (m, 2H);

^{13}C NMR (100 MHz, CDCl_3) δ 23.3 (CH_2), 33.2 (CH_2), 37.8 (CH_2), 115.3 (CH_2), 128.0 (CH), 128.6 (CH), 132.9 (CH), 137.1 (C), 138.0 (CH), 200.2 (C).

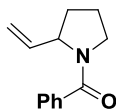


7-Bromo-1-phenylhept-5-en-1-one. According to the general procedure **I**, 1-phenylhex-5-en-1-one (3.48 g, 20 mmol), HG-2 (125 mg, 0.2 mmol, 1 mol%) and allyl bromide (5.1 mL, 60.0 mmol) afforded 7-bromo-1-phenylhept-5-en-1-one (colorless oil, 2.86 mg, 54%, *E/Z*: 15:1) as a colorless oil after column chromatography (0.5-3% EtOAc/hexanes). *E* isomer: R_f = 0.30 (5% EtOAc/hexanes); IR (neat): 2937, 1684, 1449 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.83-1.90 (m, 2H), 2.18 (q, J = 7.2 Hz, 2H), 2.98 (t, J = 7.2 Hz, 2H), 3.95 (d, J = 6.8 Hz, 2H), 5.70-5.83 (m, 2H), 7.46-7.49 (m, 2H), 7.54-7.58 (m, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.2 (CH_2), 31.5 (CH_2), 33.3 (CH_2), 37.5 (CH_2), 127.3 (CH), 128.0 (CH), 128.6 (CH), 133.0 (CH), 135.6 (CH), 137.0 (C), 200.0 (C). *Z* isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 4.01 (d, J = 8.4 Hz, 2H).



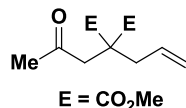
(*E*)-7-Azido-1-phenylhept-5-en-1-one (2-156a), (*Z*)-7-azido-1-phenylhept-5-en-1-one (2-156b) and 5-azido-1-phenylhept-6-en-1-one (2-156c). According to the general procedure **II**, 7-bromo-1-phenylhept-5-en-1-one (1.40 g, 5.24 mmol) and sodium azide (1.02 g, 15.7 mmol) afforded a mixture of azides **2-156a**, **2-156b**, and **2-156c** (colorless oil, 940 mg, 78%, 68:7:25 from ^1H NMR in CDCl_3) after column chromatography (0.5-3% EtOAc/hexanes). Azides **2-156a**, **2-156b**, and **2-156c**: R_f = 0.35 (10% EtOAc/hexanes); IR

(neat): 2938, 2099, 1684 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{26}\text{H}_{31}\text{N}_4\text{O}_2$ ($2\text{M}-\text{N}_2$)⁺ 431.2447, found: 431.2445. Azide **2-156a**: ^1H NMR (400 MHz, CDCl_3) δ 1.81-1.92 (m, 2H), 2.22 (q, $J = 6.8$ Hz, 2H), 2.99-3.04 (m, 2H), 3.72 (d, $J = 6.4$ Hz, 2H), 5.56-5.61 (m, 1H), 5.75-5.82 (m, 1H), 7.46-7.49 (m, 2H), 7.56-7.60 (m, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.3 (CH_2), 31.7 (CH_2), 37.6 (CH_2), 52.8 (CH_2), 123.8 (CH), 128.0 (CH), 128.6 (CH), 133.01 (CH), 136.0 (CH), 137.0 (C), 200.0 (C). Azide **2-156b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.83 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.8 (CH_2), 26.8 (CH_2), 47.1 (CH_2), 123.1 (CH), 135.3 (CH), 136.9 (C), 199.8 (C). Azide **2-156c** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.62-1.68 (m, 2H), 1.81-1.92 (m, 2H), 3.90 (q, $J = 6.8$ Hz, 1H), 5.29-5.34 (m, 2H), 5.75-5.82 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5 (CH_2), 33.8 (CH_2), 37.9 (CH_2), 64.9 (CH), 118.4 (CH_2), 128.0 (CH), 128.6 (CH), 133.08 (CH), 135.5 (CH), 136.87 (CH), 199.6 (CH).

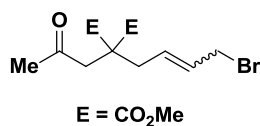


Phenyl(2-vinylpyrrolidin-1-yl)methanone (2-157). According to the general procedure **VI**, azides **2-156a**, **2-156b**, and **2-156c** (91 mg, 0.40 mmol) and titanium tetrachloride (1.2 mL, 1 M in dichloromethane, 1.2 mmol) at room temperature afforded lactam **2-157** (colorless oil, 20 mg, 25%) after column chromatography (5-30% EtOAc/hexanes). Lactam **2-157**: $R_f = 0.40$ (100% EtOAc/hexanes); IR (neat): 2972, 1627, 1409 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{16}\text{NO}$ ($\text{M}+\text{H}$)⁺ 202.1232, found: 202.1231; ^1H NMR (two rotamers with 1:1 ratio, 400 MHz, CDCl_3 , both rotamers) δ 1.75-2.20 (m, 8H), 3.40-3.80 (m, 4H), 4.37 (br, 1H), 4.85 (br, 1H), 4.93-5.28 (m, 4H), 5.68 (br, 1H), 5.92 (m, 1H), 7.35-7.54 (m, 10H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.5, 24.7, 31.0, 32.1, 45.9, 50.0,

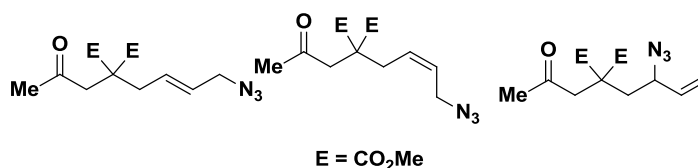
58.8, 61.5, 114.4, 115.3, 126.8, 127.2, 128.0, 128.2, 129.6, 129.8, 137.3, 137.3, 137.7, 138.3, 169.9, 170.6.



Dimethyl 2-allyl-2-(2-oxopropyl)malonate. To a solution of chloroacetone (1.2 g, 13 mol) in DMF (10 mL) at room temperature was added sodium iodide (2.10 g, 14 mmol). The reaction was stirring for 1 h. To a suspension of sodium hydride (480 mg, 60% in petroleum oil, 12 mmol) in DMF (10 mL) at 0 °C was added dimethyl 2-allylmalonate (1.72 g, 10 mmol). The stirring was continued for 1 h, followed by the addition of the above suspension. The reaction mixture was stirred overnight. The reaction mixture was quenched with saturated NH_4Cl . After the separation, the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate. After the filtration and concentration, the residue was purified by column chromatography (10-15% EtOAc/hexanes) to afford dimethyl 2-allyl-2-(2-oxopropyl)malonate (1.77 g, 78%) as a colorless oil. $R_f = 0.30$ (20% EtOAc/hexanes); IR (neat): 2955, 1738, 1723, 1436 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{16}\text{O}_5\text{Na}$ ($\text{M}+\text{Na}^+$) 251.0895, found: 251.0860; ^1H NMR (400 MHz, CDCl_3) δ 2.15 (s, 3H), 2.77 (d, $J = 7.2$ Hz, 2H), 3.11 (s, 2H), 3.73 (s, 6H), 5.04-5.12 (m, 2H), 5.58-5.68 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 30.2 (CH_3), 37.8 (CH_2), 45.7 (CH_2), 52.7 (CH_3), 54.9 (C), 119.5 (CH_2), 132.7 (CH), 170.8 (C), 205.1 (C).

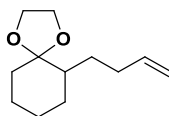


Dimethyl 2-(4-bromobut-2-en-1-yl)-2-(2-oxopropyl)malonate. According to the general procedure **I**, dimethyl 2-allyl-2-(2-oxopropyl)malonate (1.43 g, 6.3 mmol), HG-2 (100 mg, 0.16 mmol) and allyl bromide (1.7 mL, 15 mmol) afforded dimethyl 2-(4-bromobut-2-en-1-yl)-2-(2-oxopropyl)malonate (colorless oil, 1.19 g, 59%, *E/Z*: 15:1) by chromatography (3-15% EtOAc/hexanes). $R_f = 0.20$ (20% EtOAc/hexanes); IR (neat): 2954, 1738, 1723, 1435 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{17}\text{BrO}_5\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 343.0157, found: 343.0138; ^1H NMR (400 MHz, CDCl_3) δ 2.14 (s, 3H), 2.75 (d, $J = 7.2$ Hz, 2H), 3.09 (s, 2H), 3.71 (s, 6H), 3.87 (d, $J = 7.2$ Hz, 2H), 5.58-5.74 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 30.2 (CH_3), 32.1 (CH_2), 35.9 (CH_2), 45.8 (CH_2), 52.8 (CH_3), 55.0 (C), 130.0 (CH), 131.0 (CH), 170.5 (C), 205.0 (C).

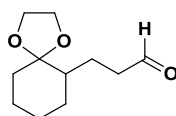


(*E*)-Dimethyl 2-(4-azidobut-2-en-1-yl)-2-(2-oxopropyl)malonate (2-168a), (*Z*)-Dimethyl 2-(4-azidobut-2-en-1-yl)-2-(2-oxopropyl)malonate (2-168b) and dimethyl 2-(2-azidobut-3-en-1-yl)-2-(2-oxopropyl)malonate (2-168c). According to the general procedure **II**, dimethyl 2-(4-bromobut-2-en-1-yl)-2-(2-oxopropyl)malonate (1.19 g, 3.7 mmol) and sodium azide (722 mg, 11.1 mmol) afforded a mixture of azides **2-168a**, **2-168b** and **2-168c** (colorless oil, 800 mg, 76%, 64:36:0 from ^1H NMR in CDCl_3) after column chromatography (10-50% EtOAc/hexanes). Azides **2-168a**, **2-168b** and **2-168c**: $R_f = 0.50$ (50% EtOAc/hexanes); IR (neat): 2955, 2102, 1735, 1720 cm^{-1} ; HRMS (ESI) m/z calculated for

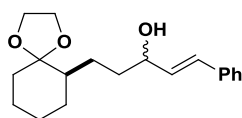
$C_{12}H_{17}N_3O_5Na$ ($M+Na$)⁺ 306.1066, found: 306.1047. Azide **2-168a**: 1H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.83 (d, $J = 6.4$ Hz, 2H), 3.14 (s, 2H), 3.72 (d, $J = 5.2$ Hz, 2H), 3.75 (s, 6H), 5.54-5.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2 (CH_3), 36.2 (CH_2), 45.8 (CH_2), 52.4 (CH_2), 52.9 (CH_3), 54.8 (C), 127.9 (CH), 130.4 (CH), 170.6 (C), 205.0 (C). Azide **2-168b**: 1H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 2.88 (dd, $J = 0.9$ Hz, 8.0 Hz, 2H), 3.14 (s, 2H), 3.73 (s, 6H), 3.79 (d, $J = 7.2$ Hz, 2H), 5.54-5.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2 (CH_3), 30.9 (CH_2), 45.6 (CH_2), 47.0 (CH_2), 52.9 (CH_3), 54.7 (C), 126.9 (CH), 128.8 (CH), 170.5 (C), 205.2 (C).



6-(But-3-enyl)-1,4-dioxaspiro(4.5)decane (2-87) To a solution of 2-(but-3-enyl)cyclohexanone (11.4 g, 75.0 mmol) and ethylene glycol (12.6 mL, 225.0 mmol) in 150 mL benzene was added p-toluenesulfonic acid monohydrate (712 mg, 3.75 mmol). The reaction mixture was heated to reflux under Dean-Stark apparatus for one day. After cooling to rt, diethyl ether and saturated aqueous sodium bicarbonate were added and the aqueous layer was washed three times with diethyl ether. The combined organic layers were washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate. The concentration afforded ketal **2-87** (13.8 g, 94%) as a colorless oil, which was used directly in the next step without further purification. Ketal **2-87**: 1H NMR (400 MHz, $CDCl_3$) δ 1.15-1.31 (m, 3H), 1.32-1.40 (m, 1H), 1.45-1.53 (m, 1H), 1.56-1.68 (m, 3H), 1.69-1.87 (m, 3H), 1.93-2.03 (m, 1H), 2.12-2.21 (m, 1H), 3.94-3.98 (m, 4H), 4.94-5.05 (m, 2H), 5.78-5.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (CH_2), 24.5 (CH_2), 27.3 (CH_2), 28.9 (CH_2), 31.7 (CH_2), 34.7 (CH_2), 44.0 (CH), 64.7 (CH_2), 64.8 (CH_2), 110.9 (C), 114.2 (CH_2), 139.3 (CH).



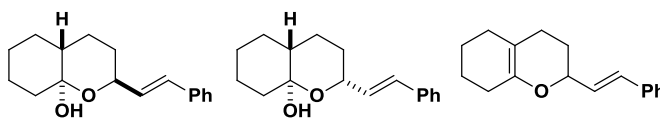
6-(3-Oxopropyl)-1,4-dioxaspiro(4.5)decane (2-88). A solution of ketal **2-87** (13.8 g, 70.3 mmol) in anhydrous dichloromethane (180 mL) was cooled to -78 °C. In-situ generated ozone was flushed into the above solution until it turned blue. N₂ was used to flush out the extra ozone. PPh₃ (27.7 g, 105 mmol) was added at -78 °C and the resulting mixture was stirred overnight and raised to rt. The solvent was removed in vacuo and the residue was applied to filtration. Hexane was used to wash the cake, followed by the washing with 5% EtOAc/hexanes. The filtrate was concentrated and the residue was purified by chromatography (2.5-20% EtOAc/hexanes) to afford aldehyde **2-88** (11.6 g, 84%) as a colorless oil. Aldehyde **2-88**: *R_f* = 0.65 (10% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 1.23-1.35 (m, 3H), 1.40-1.50 (m, 2H), 1.50-1.63 (m, 3H), 1.71-1.81 (m, 2H), 1.95-2.05 (m, 1H), 2.38-2.60 (m, 2H), 3.92-4.01 (m, 4H), 9.77 (t, *J* = 1.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 20.9 (CH₂), 23.7 (CH₂), 24.6 (CH₂), 29.2 (CH₂), 34.5 (CH₂), 42.3 (CH₂), 44.0 (CH), 64.6 (CH₂), 64.7 (CH₂), 110.6 (C), 203.1 (CH).



(E)-6-(3-Hydroxy-5-phenylpent-4-enyl)-1,4-dioxaspiro(4.5)decane (2-89). To a stirred solution of (*E*)-β-styryltributyltin (4.33 g, 11.0 mmol) in anhydrous THF (60 mL) at -78 °C under N₂ atmosphere was slowly added n-BuLi (4.4 mL, 2.5 M in hexane, 11.0 mmol). The reaction mixture turned gradually from purple to darkpurple. After stirring at -78 °C for 1 h, a solution of aldehyde **2-88** (1.60 g, 8.0 mmol) in THF (10 mL) was slowly added. The reaction mixture turned gradually yellow. After stirring overnight and warmed to rt, saturated

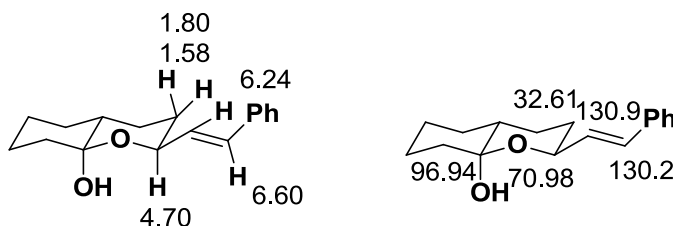
NH₄Cl was added. Diethyl ether was used to extract the product and the aqueous layer was washed twice with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄. The concentrated residue was purified by chromatography (5-30% EtOAc/hexanes) to afford alcohol **2-89** (2.37 g, 98%, ratio: 1:1) as a colorless oil.

Alcohol **2-89**: R_f = 0.55 (100% EtOAc/hexanes); IR (neat): 3413, 2932, 748, 694 cm⁻¹; HRMS (ESI) m/z calculated for C₁₉H₂₆O₃Na (M+Na)⁺ 325.1780; found: 325.1801; ¹H NMR (400 MHz, CDCl₃) δ 1.11-1.41 (m, 4H), 1.45-1.55 (m, 1H), 1.56-1.69 (m, 4H), 1.70-1.93 (m, 4H), 3.91-4.01 (m, 4H), 4.25-4.34 (m, 1H), 6.22 (dd, J = 5.2 Hz, 6.4 Hz, 1H), 6.26 (dd, J = 5.2 Hz, 6.4 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 7.23-7.27 (m, 1H), 7.33 (t, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 23.8 (CH₂), 24.1 (CH₂), 24.2 (CH₂), 24.5 (CH₂), 29.35 (CH₂), 29.38 (CH₂), 34.52 (CH₂), 34.58 (CH₂), 35.5 (CH₂), 35.6 (CH₂), 44.3 (CH), 44.6 (CH), 64.6 (CH), 64.7 (CH), 73.0 (CH₂), 73.6 (CH₂), 110.88 (C), 110.92 (C), 126.45 (CH), 126.46 (CH), 127.54 (CH), 127.57 (CH), 128.6 (CH), 130.0 (CH), 130.2 (CH), 132.6 (CH), 132.7 (CH), 136.84 (C), 136.86 (C).



(**2S*,4aR*,8aS*,E**)-2-Styryl-octahydro-2H-chromen-8a-ol (**2-92**), (**2R*,4aR*,8aS*,E**)-2-styryl-octahydro-2H-chromen-8a-ol (**2-93**), and (**E**)-2-styryl-3,4,5,6,7,8-hexahydro-2H-chromene (**2-94**). To a solution of ketal **2-89** (2.26 g, 7.47 mmol) in acetone (100 mL) at rt was added p-toluenesulfonic acid monohydrate (57 mg, 0.15 mmol). After stirring for one day, saturated NaHCO₃ was added and acetone was removed in vacuo. The aqueous layer was washed three times with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄. The concentrated residue was purified

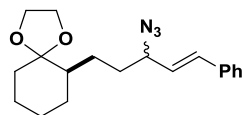
by chromatography (0.3-5% EtOAc/hexanes) to afford alcohol **2-92** (425 mg, 21%) as a white semi-solid, alcohol **2-93** (160 mg, 8%) as a white semi-solid, and olefin **2-94** (370 mg, 18%) as a colorless oil. Alcohol **2-92**: R_f = 0.50 (20% EtOAc/hexanes); IR (neat): 3419, 2929, 944, 748, 692 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{22}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 281.1518, found: 281.1504; ^1H NMR (400 MHz, CDCl_3) δ 1.28-1.83 (m, 13H), 4.67-4.72 (m, 1H), 6.24 (dd, J = 6.8 Hz, 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H), 7.21-7.26 (m, 1H), 7.28-7.33 (m, 2H), 7.40-7.42 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.3 (CH_2), 25.2 (CH_2), 26.0 (CH_2), 29.5 (CH_2), 32.6 (CH_2), 39.3 (CH_2), 43.1 (CH), 71.0 (CH), 96.9 (C), 126.5 (CH), 127.4 (CH), 128.5 (CH), 130.2 (CH), 130.9 (CH), 137.0 (C). The following data were used to assign alcohol **2-92**.



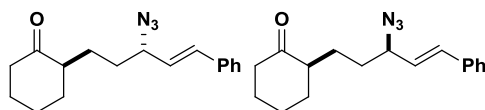
Alcohol **2-93**: R_f = 0.45 (20% EtOAc/hexanes); IR (neat): 3443, 2925, 1693, 747, 691 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{22}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 281.1518, found: 281.1520; ^1H NMR (400 MHz, CDCl_3) δ 1.40-1.52 (m, 3H), 1.53-1.80 (m, 6H), 1.81-1.92 (m, 2H), 2.27-2.36 (m, 2H), 4.67-4.72 (m, 1H), 6.27 (dd, J = 6.4 Hz, 16.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 7.21-7.26 (m, 1H), 7.28-7.33 (m, 2H), 7.40-7.42 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.6 (CH_2), 24.0 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 27.7 (CH_2), 37.3 (CH), 40.7 (CH_2), 71.0 (CH), 96.5 (C), 126.5 (CH), 127.4 (CH), 128.5 (CH), 129.7 (CH), 131.3 (CH), 137.1 (C).

Olefin **2-94**: R_f = 0.70 (20% EtOAc/hexanes); IR (neat): 2925, 1694, 748, 692 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{17}\text{H}_{21}\text{O}$ ($\text{M}+\text{H}$) $^+$ 241.1592, found: 241.1599; ^1H NMR (400 MHz,

CDCl₃) δ 1.53-1.61 (m, 1H), 1.61-1.72 (m, 2H), 1.73-1.84 (m, 2H), 1.88-2.03 (m, 4H), 2.05-2.13 (m, 3H), 4.43-4.48 (m, 1H), 6.31 (dd, J = 6.4 Hz, 16.0 Hz, 1H), 6.65 (d, J = 16.0 Hz, 1H), 7.24-7.28 (m, 1H), 7.32-7.35 (m, 2H), 7.42-7.44 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 23.0 (CH₂), 23.2 (CH₂), 25.2 (CH₂), 27.5 (CH₂), 28.8 (CH₂), 28.9 (CH₂), 75.3 (CH), 104.4 (C), 126.5 (CH), 127.6 (CH), 128.5 (CH), 129.7 (CH), 130.8 (CH), 136.9 (C), 146.3 (C).



(E)-6-(3-Azido-5-phenylpent-4-enyl)-1,4-dioxaspiro(4.5)decane (2-90). To a suspension of alcohol **2-89** (700 mg, 2.33 mmol), PPh₃ (1220 mg, 4.66 mmol), and Zn(N₃)₂·2Pyr (717 mg, 2.0 mmol) in benzene (70 mL) at rt under N₂ atmosphere was slowly added DEAD (2.03 g, 40% in toluene, 4.66 mmol). The resulting mixture was heated to reflux for 48 h. The reaction was cooled to rt and the solvent was removed in vacuo. The residue was purified by chromatography (2-5% EtOAc/hexanes) to afford azide **2-90** (350 mg, 46%, ratio: 1:1) as a colorless oil. Azide **2-90**: R_f = 0.55 (20% EtOAc/hexanes); IR (neat): 2934, 2093, 749, 694 cm⁻¹; HRMS (ESI) m/z calculated for C₁₉H₂₅N₃O₂Na (M+Na)⁺ 350.1844, found: 350.1859; ¹H NMR (400 MHz, CDCl₃) δ 1.11-1.40 (m, 4H), 1.45-1.84 (m, 9H), 3.90-4.02 (m, 5H), 6.09-6.17 (m, 1H), 6.61-6.65 (m, 1H), 7.27-7.31 (m, 1H), 7.34-7.38 (m, 2H), 7.41-7.44 (m, 2H); ¹³C NMR (100 MHz, acetone) δ 23.6 (CH₂), 24.4 (CH₂), 24.6 (CH₂), 24.7 (CH₂), 29.1 (CH₂), 29.2 (CH₂), 32.87 (CH₂), 32.89 (CH₂), 34.4 (CH₂), 44.30 (CH), 44.31 (CH), 64.32 (CH₂), 64.33 (CH₂), 64.5 (CH₂), 65.1 (CH), 65.2 (CH), 110.2 (C), 126.6 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.6 (CH), 133.0 (CH), 133.1 (CH), 136.6 (C).

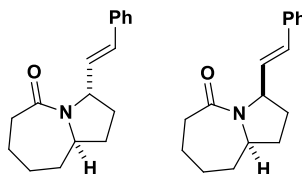


(*R*^{*})-2-((*S*^{*},*E*)-3-Azido-5-phenylpent-4-enyl)cyclohexanone (2-91a) and (*R*^{*})-2-(((*R*^{*},*E*)-3-azido-5-phenylpent-4-enyl)cyclohexanone (2-91b). *Procedure 1:* To a solution of azide **2-90** (376 mg, 1.15 mmol) in acetone at rt was added I₂ (50 mg, 0.2 mmol). After stirring for 25 min, 5% aqueous Na₂S₂O₃ was added and acetone was removed in vacuo. Diethyl ether was added and the aqueous layer was washed three times with diethyl ether. The combined organic layers were washed with 5% aqueous Na₂S₂O₃, brine, dried over anhydrous sodium sulfate. The concentrated residue was purified by chromatography (0.6-5% EtOAc/hexanes) to afford a mixture of azide **2-91a** and **2-91b** (220 mg, 68%, 1:1 ratio) as a colorless oil. Azide **2-91a** and **2-91b**: *R*_f = 0.30 (10% EtOAc/hexanes); IR (neat): 2933, 2093, 1707, 751, 694 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₇H₂₁N₃ONa (M+Na)⁺ 306.1582, found: 306.1580. Azide **2-91a**: ¹H NMR (400 MHz, CDCl₃) δ 1.28-1.47 (m, 2H), 1.57-1.74 (m, 4H), 1.81-1.93 (m, 2H), 2.05-2.18 (m, 2H), 2.28-2.37 (m, 2H), 2.38-2.45 (m, 1H), 3.99-4.07 (m, 1H), 6.13 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H); 6.64 (d, *J* = 16.0 Hz, 1H), 7.27-7.31 (m, 1H), 7.34-7.38 (m, 2H), 7.41-7.44 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 25.0 (CH₂), 25.8 (CH₂), 28.0 (CH₂), 32.3 (CH₂), 34.1 (CH₂), 42.1 (CH₂), 50.4 (CH), 65.0 (CH), 126.7 (CH), 126.9 (CH), 128.1 (CH), 128.6 (CH), 133.4 (CH), 136.0 (C), 212.7 (C). Azide **2-91b** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 6.14 (dd, *J* = 8.0 Hz, 16.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 25.1 (CH₂), 26.1 (CH₂), 28.1 (CH₂), 32.6 (CH₂), 34.3 (CH₂), 42.2 (CH₂), 50.5 (CH), 65.1 (CH), 127.0 (CH), 133.4 (CH), 212.8 (C).

Procedure 2: According to the procedure described for azide **2-90**, the reaction of alcohol **2-92** (52 mg, 0.2 mmol), PPh₃ (105 mg, 0.4 mmol), Zn(N₃)₂·2Pyr (46 mg, 0.15 mmol),

and DEAD (174 mg, 40% in toluene, 0.4 mmol) in benzene (5 mL) after chromatography (0.5-2.2% EtOAc/hexanes) afforded a mixture of azide **2-91a** and **2-91b** (34 mg, 60%, 1:2 ratio).

Procedure 3: According to the procedure described for azide **2-90**, the reaction of alcohol **2-93** (53 mg, 0.2 mmol), PPh₃ (105 mg, 0.4 mmol), Zn(N₃)₂·2Pyr (46 mg, 0.15 mmol), and DEAD (174 mg, 40% in toluene, 0.4 mmol) in benzene (5 mL) after chromatography (0.5-2.2% EtOAc/hexanes) afforded a mixture of azide **2-91a** and **2-91b** (31 mg, 53%, 2:1 ratio).



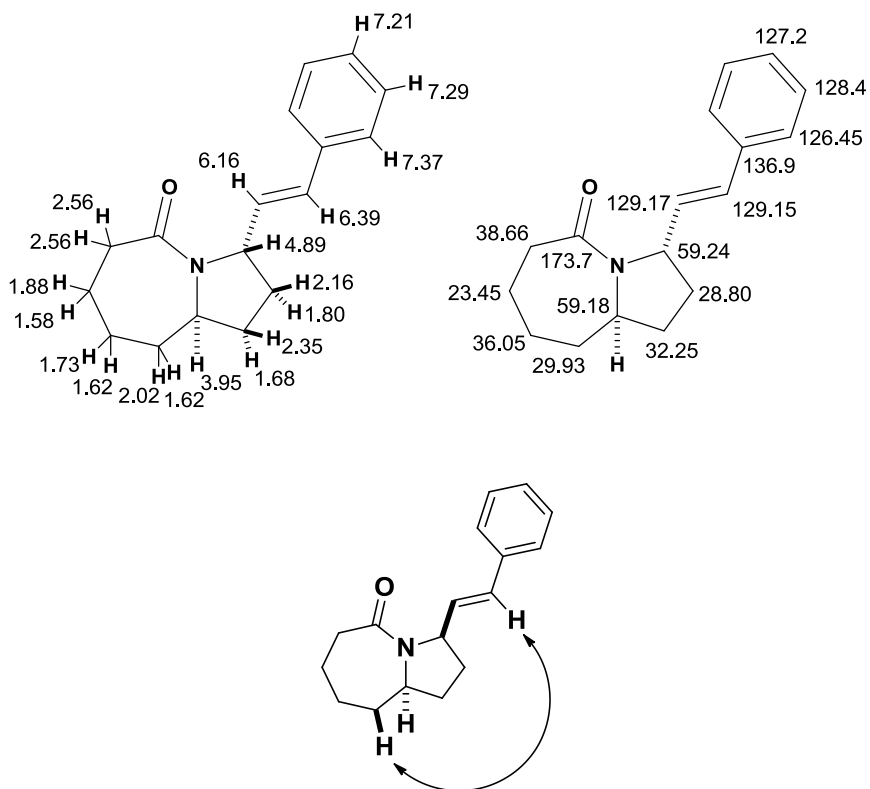
(3*S,9*aR**,*E*)-3-Styryl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2-95a)**

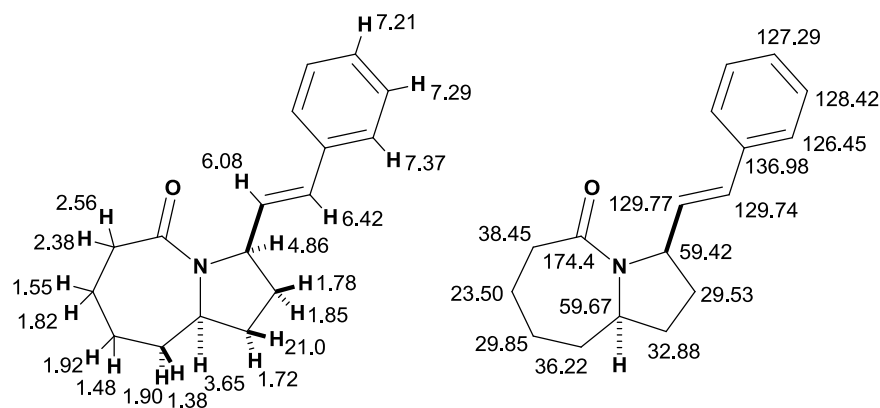
and **(3*R**,9*aR**, *E*)-3-styryl-hexahydro-1*H*-pyrrolo[1,2-*a*]azepin-5(6*H*)-one (2-95b).**

Procedure 1: According to the procedure V, the reaction of azides **2-91a** and **2-91b** (20 mg, 0.07 mmol, 2:1 ratio) and tin tetrachloride (0.14 mL, 1 M in dichloromethane, 0.14 mmol) in anhydrous dichloromethane (10 mL) after chromatography (15-200% EtOAc/hexanes) afforded lactam **2-95a** (8 mg, 44%) as a colorless oil and lactam **2-95b** (1 mg, 6%) as a colorless oil. Lactam **2-95a**: *R_f* = 0.65 (100% EtOAc); IR (neat): 2926, 1630, 1446, 1413, 728, 694 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₇H₂₁NONa (M+Na)⁺ 278.1521, found: 278.1490; ¹H NMR (400 MHz, CDCl₃) δ 1.54-1.63 (m, 3H), 1.63-1.82 (m, 3H), 1.85-1.92 (m, 1H), 1.98-2.04 (m, 1H), 2.08-2.19 (m, 1H), 2.29-2.39 (m, 1H), 2.52-2.59 (m, 2H), 3.94 (t, *J* = 9.2 Hz, 1H), 4.88 (t, *J* = 6.8 Hz, 1H), 6.16 (dd, *J* = 5.6 Hz, 16.0 Hz, 1H), 6.39 (dd, *J* = 0.8 Hz, 16.0 Hz, 1H), 7.18-7.22 (m, 1H), 7.26-7.31 (m, 2H), 7.35-7.38 (m, 2H); ¹³C NMR (100 MHz,

CDCl₃) δ 23.5 (CH₂), 28.8 (CH₂), 29.9 (CH₂), 32.3 (CH₂), 36.1 (CH₂), 38.7 (CH₂), 59.18 (CH), 59.24 (CH), 126.5 (CH), 127.2 (CH), 128.4 (CH), 129.17 (CH), 129.25 (CH), 136.9 (C), 173.7 (C). Lactam **2-95b**: R_f = 0.55 (100% EtOAc); IR (neat): 2925, 1636, 1447, 1413, 693 cm⁻¹; HRMS (ESI) m/z calculated for C₁₇H₂₁NONa (M+Na)⁺ 278.1521, found: 278.1501; ¹H NMR (500 MHz, CDCl₃) δ 1.35-1.60 (m, 3H), 1.65-1.79 (m, 2H), 1.82-1.95 (m, 4H), 2.07-2.12 (m, 1H), 2.35-2.40 (m, 1H), 2.56 (dd, J = 7.2 Hz, 14.2 Hz, 1H), 3.64-3.69 (m, 1H), 4.86 (t, J = 6.5 Hz, 1H), 6.08 (dd, J = 5.0 Hz, 15.5 Hz, 1H), 6.42 (dd, J = 1.5 Hz, 15.5 Hz, 1H), 7.12-7.16 (m, 1H), 7.20-7.24 (m, 2H), 7.28-7.30 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 23.5 (CH₂), 29.5 (CH₂), 29.9 (CH₂), 32.9 (CH₂), 36.3 (CH₂), 38.5 (CH₂), 59.4 (CH), 59.7 (CH), 126.4 (CH), 127.3 (CH), 128.4 (CH), 129.7 (CH), 129.8 (CH), 137.0 (C), 174.4 (C).

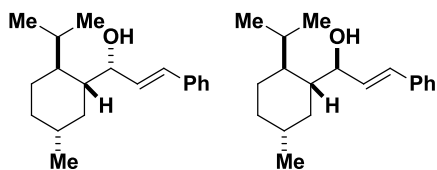
The following data and NOE correlation were used to assign lactam **2-95a** and **2-95b**.





Procedure 2: According to the general procedure **VI**, the reaction of azide **2-91a** and **2-91b** (24 mg, 0.08 mmol, 1:2 ratio) and tin chloride (0.16 mL, 1 M in dichloromethane, 0.16 mmol) in anhydrous dichloromethane (10 mL) after chromatography (15-200% EtOAc/hexanes) afforded lactam **2-95a** (9 mg, 42%) as a colorless oil and lactam **2-95b** (2 mg, 9%) as a colorless oil.

Procedure 3: According to the general procedure **VI**, the reaction of azide **2-91a** and **2-91b** (93 mg, 0.33 mmol, 1:1 ratio) and tin chloride (0.49 mL, 1 M in dichloromethane, 0.49 mmol) in anhydrous dichloromethane (12 mL) after chromatography (12-36% EtOAc/hexanes) afforded lactam **2-95a** (35 mg, 42%) as a colorless oil and lactam **2-95b** (5 mg, 6%) as a colorless oil.

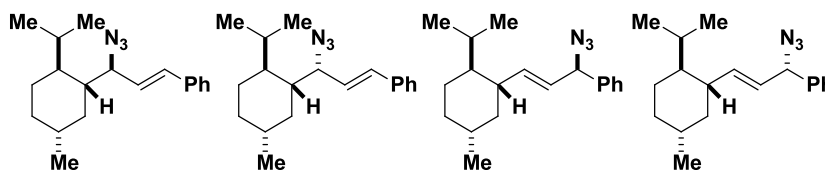


(*R,E*)-1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-3-phenylprop-2-en-1-ol

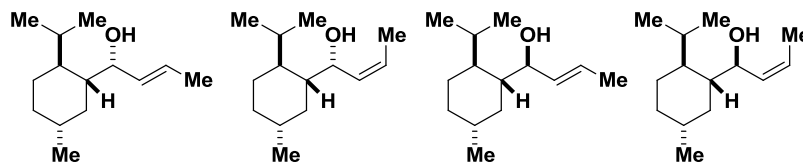
and **(*S,E*)-1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-3-phenylprop-2-en-1-ol**.

According to the procedure described for alcohol **2-89**, (1*R*,2*S*,5*R*)-2-isopropyl-5-

methylcyclohexanecarbaldehyde (260 mg, 1.55 mmol) and (*E*)- β -styryltributyltin (865 mg, 2.20 mmol) afforded (*R,E*)-1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-3-phenylprop-2-en-1-ol (186 mg, 44%) as a colorless oil and (*S,E*)-1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-3-phenylprop-2-en-1-ol (106 mg, 25%) as a colorless oil after column chromatography (2.5% EtOAc/hexanes). Their spectral data matched with reported data.⁹⁴

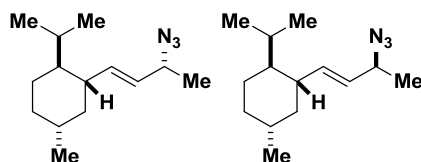


((*S,E*)-3-Azido-3-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)prop-1-en-1-yl)benzene (2-189a), ((*R,E*)-3-azido-3-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)prop-1-en-1-yl)benzene (2-189b), ((*R,E*)-1-azido-3-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)allyl)benzene (2-189c), and ((*S,E*)-1-azido-3-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)allyl)benzene (2-189d). According to the procedure described for azide 90, (*R,E*)-1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-3-phenylprop-2-en-1-ol (186 mg, 0.683 mmol) afforded a mixture of azides 2-189a, 2-189b, 2-189c, and 2-189d (120 mg, 59%, (2-189a+2-189b):(2-189c+2-189d) = 8.9:1; 2-189a:2-189b = 2.5:1) as a colorless oil after column chromatography (0-2.5% EtOAc/hexanes). Their spectral data matched with reported data.⁹⁴

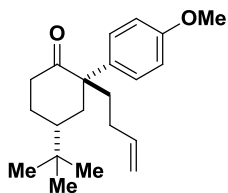


(*R,E*)-1-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)but-2-en-1-ol (2-320a), (*R,Z*)-1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)but-2-en-1-ol (2-320b), (*S,E*)-1-

((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)but-2-en-1-ol (**2-320c**) and (*S,Z*)-1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)but-2-en-1-ol (**2-320d**). A solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanecarbaldehyde (890 mg, 5.30 mmol) was slowly added to prop-1-en-1-ylmagnesium bromide (0.5 M in THF, 26.5 mL, 13.2 mmol) at -78 °C under N₂ atmosphere. After warming naturally to the room temperature, the reaction was quenched with aqueous saturated ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were washed with brine, and then dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (1-5% EtOAc/hexanes) to afford a mixture of alcohols **2-320a** and **2-320b** (100 mg, 9%, 1:0.14 ratio) as a colorless oil, a mixture of alcohols **2-320a** and **2-320b** (150 mg, 13%, 1:10 ratio) as a colorless oil, a mixture of alcohols **2-320b**, **2-320c** and **2-320d** (35 mg, 3%, 0.5:1:0.15 ratio) as a colorless oil, and a mixture of alcohols **2-320c** and **2-320d** (25 mg, 2%, 1:0.3 ratio) as a colorless oil. Their spectral data matched with reported data.⁹⁴

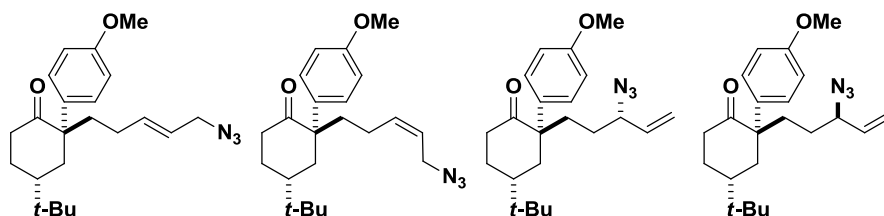


(1*S*,2*S*,4*R*)-2-((*R,E*)-3-Azidobut-1-en-1-yl)-1-isopropyl-4-methylcyclo-hexane (**2-298a**), and (1*S*,2*S*,4*R*)-2-((*S,E*)-3-azidobut-1-en-1-yl)-1-isopropyl-4-methylcyclo-hexane (**2-298b**). According to the procedure described for azide **90**, alcohols **2-320a** and **2-320b** (150 mg, 1:10 ratio, 0.71 mmol) afforded a mixture of azides **2-298a** and **2-298b** (110 mg, 66%, 3:1 ratio) as a colorless oil after column chromatography (100% hexanes). Their spectral data matched with reported data.⁹⁴



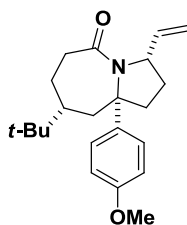
(2*S,4*R**)-2-(But-3-enyl)-4-tert-butyl-2-(4-methoxyphenyl)cyclohexanone.** To a suspension of potassium hydride (in mineral oil; washed with hexanes and dried; 1.32 g, 33 mmol) in anhydrous THF (36 mL) was added dropwise 4-(tert-butyl)-2-(4-methoxyphenyl)cyclohexanone (3.43 g, 13.2 mmol) in THF (12 mL) at room temperature and the resulting solution was stirred for 5 h, before cooling to 0 °C. 4-Iodo-1-butene (4.50 g, 25 mmol) and 4-bromo-1-butene (4.5 g, 34 mmol) were added slowly, and the resulting mixture was stirred for 20 h at room temperature and refluxed for 24 h. After cooling to room temperature, the reaction was quenched with saturated sodium bicarbonate and extracted with diethyl ether. The combined extracts were washed with brine, and dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (1-7% EtOAc/hexanes), followed by crystallization (EtOAc/hexanes) to afford (2*S**,4*R**)-2-(but-3-enyl)-4-tert-butyl-2-(4-methoxyphenyl)cyclohexanone (750 mg, 18%) as a white solid. Mp = 79-80 °C; R_f = 0.70 (20% EtOAc/hexanes); IR (neat) 2953, 1709, 1512 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{21}\text{H}_{31}\text{O}_2(\text{M}+\text{H})^+$ 315.2324, found: 315.2340; ^1H NMR (400 MHz, acetone) δ 0.98 (s, 9H), 1.55-1.70 (m, 2H), 1.76 (tdd, J = 12.0, 4.0, 3.1 Hz, 1H), 1.90-2.19 (m, 6H), 2.39 (ddd, J = 14.6, 6.5, 4.6 Hz, 1H), 2.54 (ddd, J = 14.6, 9.9, 6.9 Hz, 1H), 3.79 (s, 3H), 4.90 (ddt, J = 10.2, 2.1, 1.1 Hz, 2H), 4.97 (dq, J = 17.1, 1.6 Hz, 1H), 5.80 (ddt, J = 16.8, 10.2, 6.6 Hz, 1H), 6.89 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, acetone) δ 26.0 (CH_2), 26.8 (CH_3), 28.2 (CH_2), 32.2 (C), 34.9 (CH_2), 37.3 (CH_2), 37.8 (CH_2), 41.6 (CH), 54.5 (CH_3), 55.2 (C), 113.2 (CH), 113.9 (CH_2), 128.6 (CH_2), 134.4 (C), 138.5 (CH), 158.2

(C), 212.2 (C); ^1H NMR (500 MHz, CDCl_3) δ 0.96 (s, 9H), 1.59-1.73 (m, 3H), 1.91-2.07 (m, 6H), 2.09-2.17 (m, 2H), 2.45-2.58 (m, 2H), 3.82 (s, 3H), 4.93-4.96 (m, 1H), 4.99 (dt, $J = 17.1$, 1.6 Hz, 1H), 5.78 (ddt, $J = 16.6$, 10.1, 6.4 Hz, 1H), 6.90 (d, $J = 8.9$ Hz, 1H), 7.20 (d, $J = 8.9$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 26.5 (CH_2), 27.4 (CH_3), 28.2 (CH_2), 32.6 (C), 34.8 (CH_2), 38.0 (CH_2), 38.3 (CH_2), 41.9 (CH), 55.2 (CH_3), 55.5 (C), 113.5 (CH), 114.6 (CH_2), 128.6 (CH), 134.1 (C), 138.2 (CH), 158.0 (C), 214.2 (C).



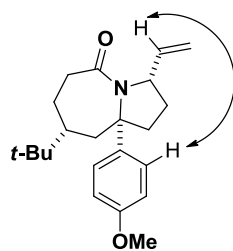
(2*S,4*R**,*E*)-2-(5-Azidopent-3-enyl)-4-tert-butyl-2-(4-methoxyphenyl)cyclohexanone (2-154a)**, **(2*S**,4*R**,*Z*)-2-(5-Azidopent-3-enyl)-4-tert-butyl-2-(4-methoxyphenyl)cyclohexanone (2-154b)**, **(2*S**,4*R**)-2-((*S**)-3-azidopent-4-enyl)-4-tert-butyl-2-(4-methoxyphenyl)cyclohexanone (2-154c)**, and **(2*S**,4*R**)-2-((*R**)-3-azidopent-4-enyl)-4-tert-butyl-2-(4-methoxyphenyl)cyclohexanone (2-154d)**. According to the general procedure **III**, (2*S**,4*R**)-2-(but-3-enyl)-4-tert-butyl-2-(4-methoxyphenyl)cyclohexanone (750 mg, 2.40 mmol), HG-2 (75 mg, 0.12 mmol) and allyl bromide (0.61 mL, 7.2 mmol) afforded a mixture of azides **2-154a**, **2-154b**, **2-154c**, and **2-154d** (510 mg, 58%, 86% brsm, 61:7:16:16 from ^{13}C NMR in CDCl_3) as a semisolid and recovered starting material (260 mg). Azides **2-154a**, **2-154b**, **2-154c**, and **2-154d**: $R_f = 0.45$ (20% EtOAc/hexanes); IR (neat) 2954, 2094, 1708, 1512 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 392.2314, found: 392.2312. Azide **2-154a**: ^1H NMR (400 MHz, acetone) δ 0.98 (s, 9H), 1.59-1.79 (m, 3H), 1.95-2.19 (m, 6H), 2.35-2.45 (m, 1H), 2.46-2.56 (m, 1H), 3.74 (d, $J = 6.0$ Hz, 1H), 3.79 (s, 3H), 5.49-5.56 (m, 1H), 5.72-5.81 (m, 1H), 6.88-6.91 (m, 2H), 7.23-7.26 (m, 2H); ^{13}C

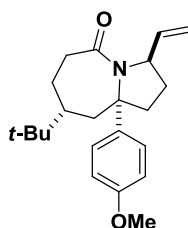
NMR (100 MHz, acetone) δ 26.0 (CH₂), 26.7 (CH₂), 26.8 (CH₃), 32.2 (C), 35.1 (CH₂), 37.3 (CH₂), 37.8 (CH₂), 41.6 (CH), 52.2 (CH₂), 54.5 (CH₃), 55.2 (C), 113.2 (CH), 123.3 (CH), 128.6 (CH), 134.3 (C), 136.0 (CH), 158.2 (C), 212.3 (C); ¹H NMR (500 MHz, CDCl₃) δ 0.963 (s, 9H), 1.58-1.71 (m, 3H), 1.92-2.19 (m, 6H), 2.45-2.52 (m, 2H), 3.69 (d, *J* = 6.6 Hz, 2H), 3.822 (s, 3H), 5.45-5.52 (m, 1H), 5.67-5.74 (m, 1H), 6.87-6.92 (m, 2H), 7.17-7.21 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 26.3 (CH₂), 26.8 (CH₂), 27.4 (CH₃), 32.6 (C), 35.2 (CH₂), 37.8 (CH₂), 38.2 (CH₂), 41.9 (CH), 52.7 (CH₂), 55.2 (CH₃), 55.4 (C), 113.6 (CH), 123.2 (CH), 128.5 (CH), 133.8 (C), 136.0 (CH), 158.1 (C), 214.1 (C). Azide **2-154b** (diagnostic peaks only): ¹³C NMR (100 MHz, acetone) δ 122.4 (CH), 134.2 (C), 135.3 (CH); ¹H NMR (500 MHz, CDCl₃) δ 0.967 (s, 9H), 3.827 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 55.5 (C), 122.5 (CH), 128.4 (CH), 133.7 (C), 135.2 (CH), 158.2 (C), 214.0 (C). Azides **2-154c** and **2-154d** (diagnostic peaks only): ¹H NMR (400 MHz, acetone) δ 3.88-3.99 (m, 1H), 5.24-5.33 (m, 2H); ¹³C NMR (100 MHz, acetone) δ 54.9 (C), 64.99 (CH), 65.04 (CH), 113.2 (CH), 117.6 (CH₂), 117.8 (CH₂), 128.6 (CH), 134.08 (C), 134.13 (C), 135.87 (CH), 135.90 (CH), 212.3 (C); ¹H NMR (500 MHz, CDCl₃) δ 0.956 (s, 9H), 3.72-3.79 (m, 1H), 3.818 (s, 3H), 5.21-5.30 (m, 2H), 5.60-5.66 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 55.1 (C), 65.1 (CH), 65.2 (CH), 113.59 (CH), 113.62 (CH), 118.4 (CH₂), 118.6 (CH₂), 128.4 (CH), 128.5 (CH), 133.7 (C), 135.27 (CH), 135.34 (CH), 158.1 (C), 158.2 (C), 214.13 (C), 214.16 (C).



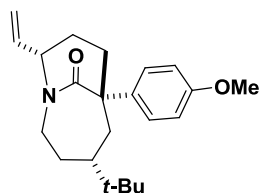
(3*S,8*R**,9*aS**)-8-(tert-Butyl)-9a-(4-methoxyphenyl)-3-vinylhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (2-155a).** According to the general procedure **VI**, a mixture

of azides **2-154a**, **2-154b**, **2-154c**, and **2-154d** (55 mg, 0.15 mmol) and MeAlCl_2 (1 M in hexanes, 0.23 mL, 0.23 mmol) in refluxing dichloroethane afforded a mixture of lactams **2-155a** and **2-155b** (3 mg, 6%, 10:1 ratio) as a white solid, and lactam **2-155c** (7 mg, 14%) as a white solid after column chromatography (6-30% EtOAc/hexanes). Amide **2-155a**: R_f = 0.30 (50% EtOAc/hexanes); IR (neat) 2959, 1638, 1510 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{32}\text{NO}_2(\text{M}+\text{H})^+$ 342.2433, found: 342.2463; ^1H NMR (500 MHz, CDCl_3) δ 0.81 (s, 9H), 1.16-1.27 (m, 3H), 1.37 (dd, J = 14.1, 10.0 Hz, 1H), 1.78-1.85 (m, 2H), 1.95-2.02 (m, 1H), 2.10 (dd, J = 12.1, 6.1 Hz, 1H), 2.16 (dd, J = 12.4, 6.1 Hz, 1H), 2.18-2.26 (m, 2H), 3.74 (s, 3H), 4.48 (dt, J = 10.0, 7.3 Hz, 1H), 5.04 (dt, J = 10.3, 1.1 Hz, 1H), 5.14 (dt, J = 17.2, 1.1 Hz, 1H), 5.89 (ddd, J = 17.3, 10.3, 7.1 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 24.7 (CH_2), 27.0 (CH_3), 27.6 (CH_2), 32.7 (C), 33.6 (CH_2), 40.81 (CH_2), 40.82 (CH_2), 41.5 (CH), 55.3 (CH_3), 62.2 (CH), 69.6 (C), 113.7 (CH), 115.6 (CH_2), 126.3 (CH), 138.9 (C), 139.4 (CH), 158.5 (C), 172.7 (C). The following NOE correlation was used to assign lactam **2-155a**.



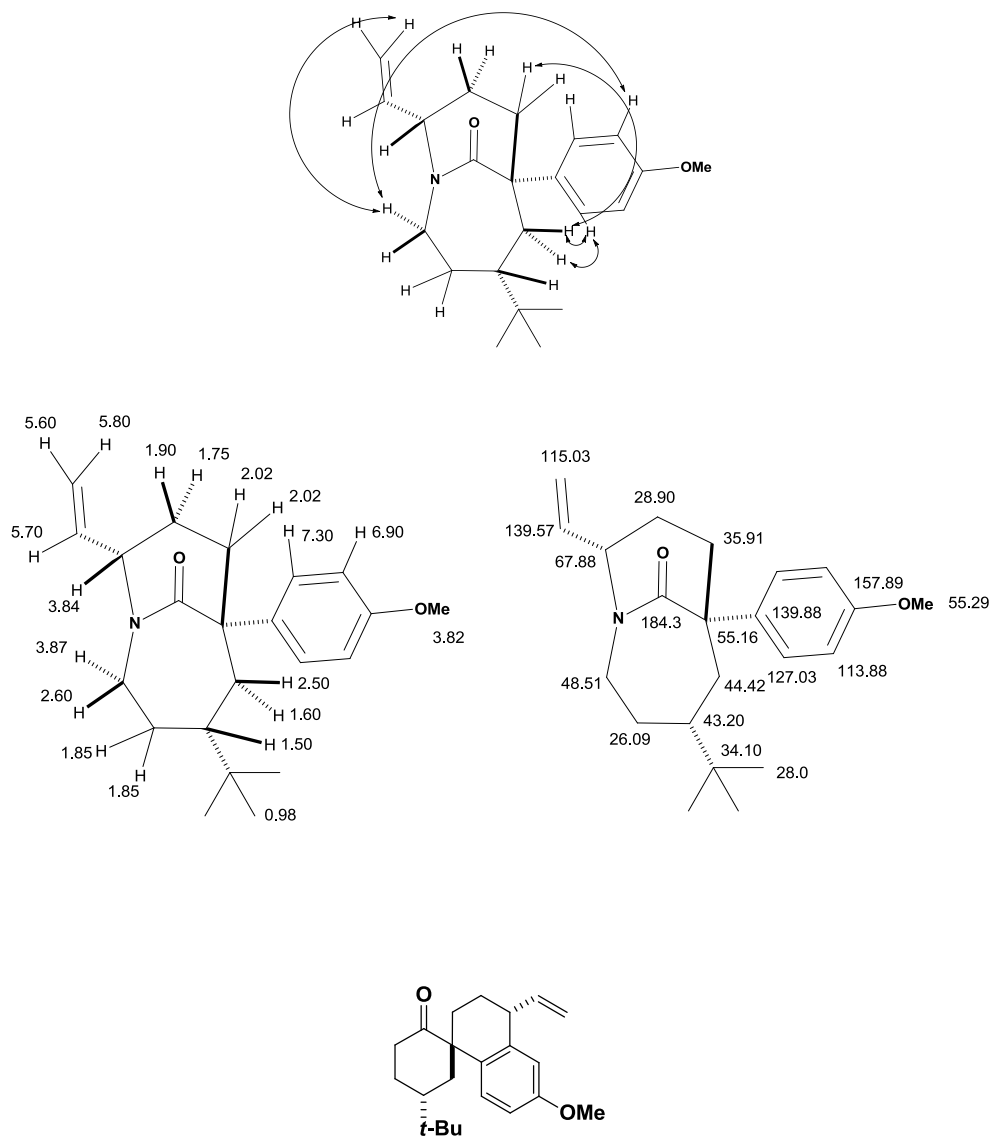


(3*R,8*R**,9*aS**)-8-(tert-Butyl)-9a-(4-methoxyphenyl)-3-vinylhexahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (2-155b).** Amide **2-155b** (diagnostic peaks only): R_f = 0.25 (50% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 0.83 (s, 9H), 1.89 (dd, J = 12.0, 5.5 Hz, 1H), 2.42 (d, J = 12.8 Hz, 1H), 3.73 (s, 3H), 4.63 (t, J = 7.5 Hz, 1H), 5.10 (dm, J = 10.4 Hz, 1H), 5.19 (dm, J = 17.3 Hz, 1H), 5.81-5.89 (m, 1H), 6.79 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 24.5 (CH_2), 27.0 (CH_2), 27.2 (CH_3), 32.6 (C), 33.7 (CH_2), 39.9 (CH_2), 41.9 (CH), 42.1 (CH_2), 55.3 (CH_3), 60.4 (CH), 68.8 (C), 113.6 (CH), 115.2 (CH_2), 126.1 (CH), 137.8 (CH), 140.2 (C), 158.3 (C), 172.6 (C).



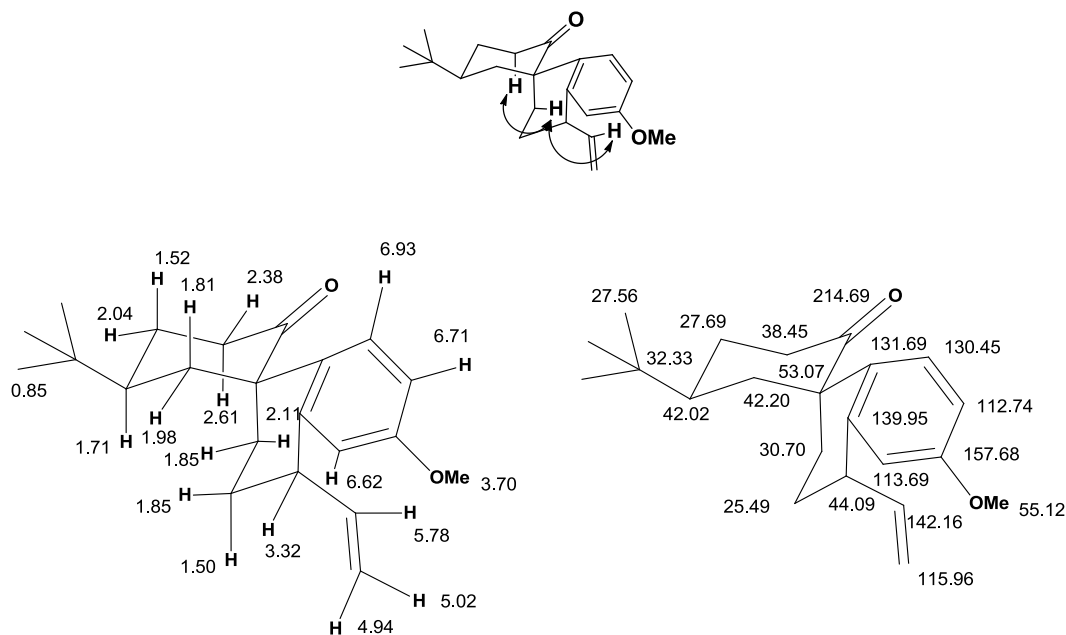
(4*S,6*S**,9*S**)-4-(tert-Butyl)-6-(4-methoxyphenyl)-9-vinyl-1-azabicyclo[4.3.1]decan-10-one (2-155c).** Twisted amide **2-155c**: R_f = 0.75 (50% EtOAc/hexanes); IR (neat) 2957, 1670, 1513 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{22}\text{H}_{32}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$ 342.2433, found: 342.2459; ^1H NMR (400 MHz, CDCl_3) δ 0.98 (s, 9H), 1.45-1.52 (m, 1H), 1.64 (d, J = 11.6 Hz, 1H), 1.67-1.79 (m, 1H), 1.81-1.97 (m, 3H), 1.99-2.06 (m, 2H), 2.50 (d, J = 11.2 Hz, 1H), 2.60 (dt, J = 13.5, 9.2 Hz, 1H), 3.82 (s, 3H), 3.83-3.88 (m, 2H), 5.11 (d, J = 10.2 Hz, 1H), 5.29 (d, J = 17.0 Hz, 1H), 5.71 (ddd, J = 16.8, 10.1, 6.5 Hz, 1H), 6.90 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.1 (CH_2), 28.0 (CH_3), 28.9 (CH_2),

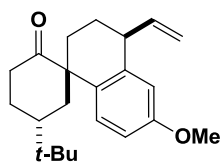
34.1 (C), 35.9 (CH₂), 43.2 (CH), 44.4 (CH₂), 48.5 (CH₂), 55.2 (C), 55.3 (CH₃), 67.9 (CH), 113.9 (CH), 115.0 (CH₂), 127.1 (CH), 139.6 (CH), 139.9 (C), 157.9 (C), 184.3 (C). The following data and NOE correlations were used to assign lactam **2-155c**.



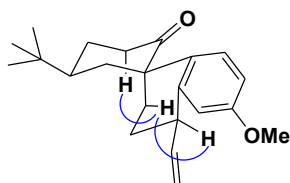
(1*S**,4'*R**,5*R**)-5-(tert-Butyl)-6'-methoxy-4'-vinyl-3',4'-dihydro-2'H-spiro[cyclohexane-1,1'-naphthalen]-2-one (**2-155g**). According to the general procedure VI, a mixture of azides **2-154a**, **2-154b**, **2-154c**, and **2-154d** (78 mg, 0.21 mmol) and SnCl₄ (1 M in

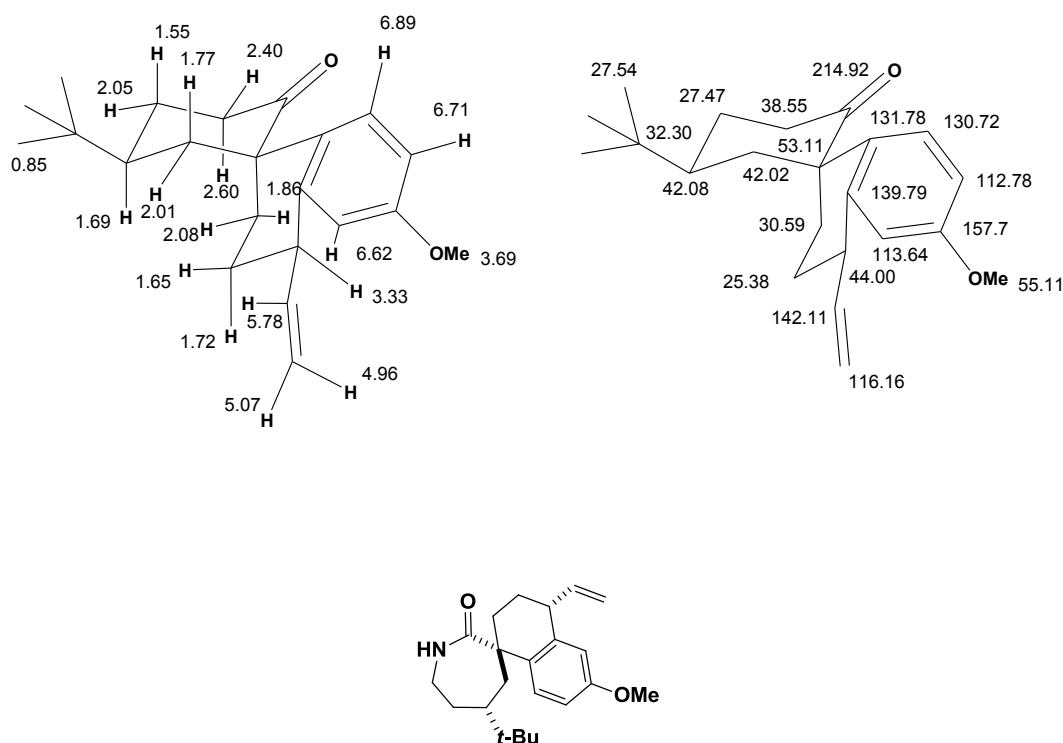
dichloromethane, 0.32 mL, 0.32 mmol) in refluxing dichloroethane afforded a mixture of lactams **2-155a** and **2-155b** (14 mg, 20%, 30:1 ratio), ketone **2-155g** (14 mg, 21%) as a colorless oil and ketone **2-155h** (7 mg, 10%) as a colorless oil after column chromatography (1-20% EtOAc/hexanes). Ketone **2-155g**: R_f = 0.30 (5% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 0.85 (s, 9H), 1.47-1.57 (m, 2H), 1.71 (tt, J = 2.8, 12.3 Hz, 1H), 1.78-1.89 (m, 3H), 1.98 (td, J = 3.0, 13.5 Hz, 1H), 2.02-2.13 (m, 2H), 2.38 (ddd, J = 2.7, 4.4, 15.5 Hz, 1H), 2.61 (ddd, J = 6.1, 14.0, 15.2 Hz, 1H), 3.32 (q, J = 7.0 Hz, 1H), 3.70 (s, 3H), 4.95 (td, J = 1.3, 17.0 Hz, 1H), 5.02 (dd, J = 1.4, 10.0 Hz, 1H), 5.74-5.81 (m, 1H), 6.62 (d, J = 2.8 Hz, 1H), 6.72 (dd, J = 2.8, 8.5 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.5 (CH_2), 27.56 (CH_3), 27.69 (CH_2), 30.7 (CH_2), 32.3 (C), 38.5 (CH_2), 42.0 (CH), 42.2 (CH_2), 44.1 (CH), 53.1 (C), 55.1 (CH), 112.7 (CH), 113.7 (CH), 116.0 (CH_2), 130.5 (CH), 131.7 (C), 140.0 (C), 142.2 (CH), 157.7 (C), 214.7 (C). The following data and NOE correlation were used to assign ketone **2-155g**.





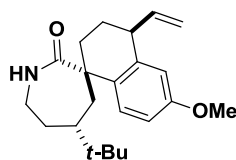
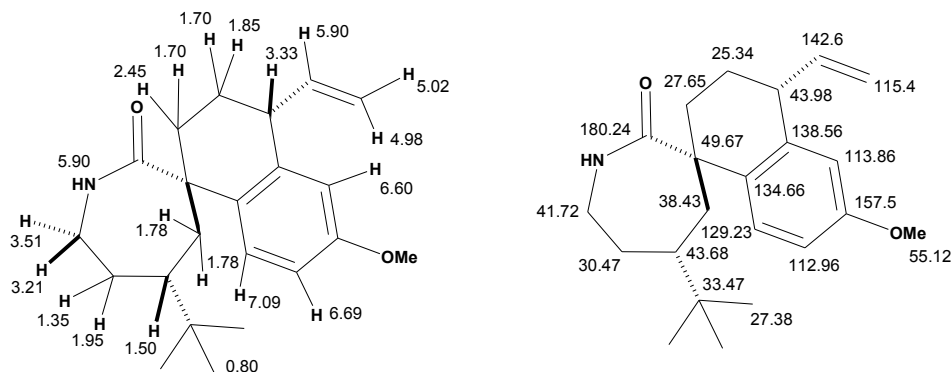
(1*S,4'*S**,5*R**)-5-(tert-butyl)-6'-methoxy-4'-vinyl-3',4'-dihydro-2'H-spiro[cyclohexane-1,1'-naphthalen]-2-one (2-155h).** Ketone **2-155h**: $R_f = 0.25$ (5% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 0.85 (s, 9H), 1.50-1.57 (m, 1H), 1.60-1.80 (m, 4H), 1.86 (ddd, $J = 2.8, 9.5, 10.4$ Hz, 1H), 1.98-2.10 (m, 3H), 2.40 (ddd, $J = 2.5, 4.5, 15.5$ Hz, 1H), 2.60 (ddd, $J = 6.0, 14.0, 15.5$ Hz, 1H), 3.33 (q, $J = 7.0$ Hz, 1H), 3.70 (s, 3H), 4.97 (td, $J = 1.5, 17.0$ Hz, 1H), 5.07 (dd, $J = 1.2, 10.0$ Hz, 1H), 5.75-5.82 (m, 1H), 6.62 (d, $J = 2.5$ Hz, 1H), 6.71 (dd, $J = 2.8, 8.5$ Hz, 1H), 6.89 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.4 (CH_2), 27.47 (CH_2), 27.54 (CH_3), 30.6 (CH_2), 32.3 (C), 38.6 (CH_2), 42.02 (CH_2), 42.08 (CH), 44.0 (CH), 53.1 (C), 55.1 (CH), 112.8 (CH), 113.6 (CH), 116.2 (CH_2), 130.7 (CH), 131.8 (C), 139.8 (C), 142.1 (CH), 157.7 (C), 214.9 (C). The following data and NOE correlation were used to assign ketone **2-155h**.





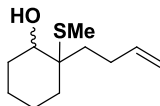
(1'*S**,4'*R**,5*S**)-5-(tert-Butyl)-6'-methoxy-4'-vinyl-3',4'-dihydro-2'*H*-spiro[azepane-3,1'-naphthalen]-2-one (**2-155e**). According to the general procedure **VI**, a mixture of azides **2-154a**, **2-154b**, **2-154c**, and **2-154d** (92 mg, 0.25 mmol) and TiCl_4 (1 M in dichloromethane, 0.38 mL, 0.38 mmol) in refluxing dichloroethane afforded a mixture of lactams **2-155a** and **2-155b** (40 mg, 20%, 50:1 ratio), lactam **2-155e** (11 mg, 13%) as a white solid, a mixture of lactams **2-155e** and **2-155f** (12 mg, 14%, 1:1 ratio) as a white solid, and lactam **2-155f** (10 mg, 12%) as a white solid after column chromatography (1-20% EtOAc/hexanes). Amide **2-155e**: R_f = 0.35 (100% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 0.80 (s, 9H), 1.31-1.38 (m, 1H), 1.48-1.55 (m, 1H), 1.66-1.73 (m, 2H), 1.74-1.82 (m, 2H), 1.83-1.90 (m, 1H), 1.92-1.98 (m, 1H), 2.44 (t, J = 10.5 Hz, 1H), 3.20-3.27 (m, 1H), 3.33 (q, J = 6.5 Hz, 1H), 3.48-3.55 (m, 1H), 3.69 (s, 3H), 4.98 (dd, J = 0.8, 17.0 Hz, 1H), 5.02 (dd, J = 1.7, 10.0 Hz, 1H), 5.85-5.93 (m, 2H), 6.60 (d, J = 2.7 Hz, 1H), 6.70 (dd, J = 2.8,

8.7 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.3 (CH_2), 27.38 (CH_3), 27.65 (CH_2), 30.1 (CH_2), 33.5 (C), 38.4 (CH_2), 41.7 (CH_2), 43.7 (CH), 44.0 (CH), 49.7 (C), 55.1 (CH), 113.0 (CH), 113.9 (CH), 115.4 (CH_2), 129.2 (CH), 134.7(C), 138.6 (C), 142.6 (CH), 157.5 (C), 180.2 (C). The following data were used to assign lactam **2-155e**.



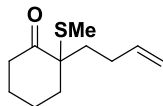
(1'S*,4'S*,5S*)-5-(tert-Butyl)-6'-methoxy-4'-vinyl-3',4'-dihydro-2'H-spiro[azepane-3,1'-naphthalen]-2-one (2-155f). Amide **2-155f**: R_f = 0.30 (100% EtOAc/hexanes); ^1H NMR (500 MHz, CDCl_3) δ 0.80 (s, 9H), 1.33-1.41 (m, 1H), 1.45-1.57 (m, 2H), 1.57-1.66 (m, 1H), 1.78 (d, J = 6.2 Hz, 1H), 1.85-2.00 (m, 3H), 2.23-2.32 (m, 1H), 3.18-3.26 (m, 1H), 3.42 (q, J = 8.2 Hz, 1H), 3.55-3.63 (m, 1H), 3.69 (s, 3H), 4.99-5.04 (m, 1H), 5.08 (dd, J = 10.1, 1.8 Hz, 1H), 5.77 (ddd, J = 17.1, 10.0, 8.2 Hz, 1H), 5.84-5.90 (m, 1H), 6.63 (d, J = 2.7 Hz, 1H), 6.69 (dd, J = 8.7, 2.9 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 25.5 (CH_2), 27.3 (CH_3), 28.3 (CH_2), 29.9 (CH_2), 33.4 (C), 38.2 (CH_2), 41.5 (CH_2), 43.3 (CH), 44.1 (CH), 49.9 (C), 55.1 (CH_3), 113.0 (CH), 113.7 (CH), 116.1 (CH_2), 129.3 (CH), 134.6 (C),

138.5 (C), 142.3 (CH), 157.6 (C), 180.5 (C). The following data were used to assign lactam **2-155f**.

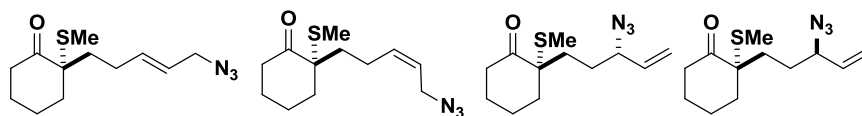


2-(But-3-en-1-yl)-2-(methylthio)cyclohexanol. To a suspension of potassium hydride (in mineral oil; washed with hexanes and dried; 1.0 g, 25 mmol) in anhydrous THF (30 mL) was added dropwise 2-(methylthio)cyclohexanone (1.44 g, 10.0 mmol) in THF (5 mL) at room temperature and the resulting solution was stirred for 3 h. 4-Iodo-1-butene (5.46 g, 30 mmol) was added slowly, and the resulting mixture was stirred for 24 h at room temperature and refluxed for 24 h. After cooling to room temperature, the reaction was quenched with saturated sodium bicarbonate and extracted with diethyl ether. The combined extracts were washed with brine, and dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (1-5% EtOAc/hexanes) to afford 2-(but-3-en-1-yl)-2-(methylthio)cyclohexanone (610 mg, 31%, 90% purity). To a solution of 2-(but-3-en-1-yl)-2-(methylthio)cyclohexanone (610 mg, 3.08 mmol) in methanol (15 mL) at 0 °C was added portionwise sodium borohydride (360 mg, 9.47 mmol). The reaction was stirred for 5 h at room temperature, followed by the addition of sodium borohydride (120 mg, 3.16 mmol). The reaction was stirred overnight, and quenched with water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (1-5% EtOAc/hexanes) to afford 2-(but-3-en-1-yl)-2-(methylthio)cyclohexanol (215 mg, 35%, one isomer) as a colorless oil. R_f = 0.45 (10% EtOAc/hexanes); IR (neat) 3454, 2931, 1640 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.36-1.77 (m, 8H), 1.85-1.95 (m, 2H), 1.94 (s, 3H), 2.10-2.21 (m, 1H),

2.25-2.35 (m, 1H), 2.88 (s, 1H), 3.53 (d, $J = 4.9$ Hz, 1H), 4.95-5.04 (m, 1H), 5.08 (dq, $J = 17.1, 1.6$ Hz, 1H), 5.88 (ddt, $J = 16.8, 10.2, 6.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 9.1 (CH_3), 20.5 (CH_2), 21.5 (CH_2), 28.0 (CH_2), 28.2 (CH_2), 29.5 (CH_2), 31.8 (CH_2), 55.1 (C), 70.4 (CH), 114.6 (CH_2), 138.6 (CH).



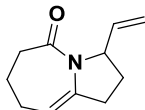
2-(But-3-en-1-yl)-2-(methylthio)cyclohexanone. According to the general procedure for the synthesis of (2*S*,5*R*)-5-methyl-2-(2-methylpent-4-en-2-yl)cyclohexanone, 2-(but-3-en-1-yl)-2-(methylthio)cyclohexanol (215 mg, 1.1 mmol) afforded 2-(but-3-en-1-yl)-2-(methylthio)cyclohexanone (63 mg, 29%) as a colorless oil after column chromatography (1-5% EtOAc/hexanes). $R_f = 0.40$ (10% EtOAc/hexanes); IR (neat) 2936, 1695, 1439 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{11}\text{H}_{19}\text{OS}$ ($\text{M}+\text{H}$) $^+$ 199.1157, found: 199.1157; ^1H NMR (400 MHz, CDCl_3) δ 1.57-1.73 (m, 3H), 1.81 (s, 3H), 1.85-1.92 (m, 2H), 1.95-2.12 (m, 4H), 2.15-2.23 (m, 1H), 2.25 (ddt, $J = 15.1, 4.3, 2.3$ Hz, 2H), 3.13 (ddd, $J = 15.1, 13.8, 6.1$ Hz, 1H), 4.95-5.00 (m, 1H), 5.06 (dq, $J = 17.1, 1.6$ Hz, 1H), 5.86 (ddt, $J = 16.8, 10.2, 6.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 11.0 (CH_3), 21.0 (CH_2), 26.3 (CH_2), 27.7 (CH_2), 32.3 (CH_2), 36.1 (CH_2), 36.9 (CH_2), 56.4 (C), 114.6 (CH_2), 138.5 (CH), 206.6 (C).



(*S,*E*)-2-(5-Azidopent-3-enyl)-2-(methylthio)cyclohexanone (2-138a)**, **(*S**,*Z*)-2-(5-azidopent-3-enyl)-2-(methylthio)cyclohexanone (2-138b)**, **(*S**)-2-((*S**)-3-azidopent-4-enyl)-2-(methylthio)cyclohexanone (2-138c)**, and **(*S**)-2-((*R**)-3-azidopent-4-enyl)-2-**

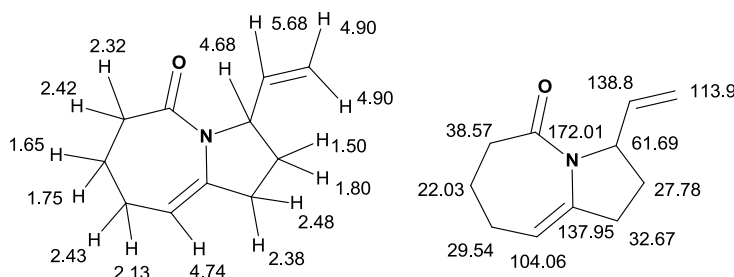
(methylthio)cyclohexanone (2-138d). According to the general procedure **III**, 2-(but-3-en-1-yl)-2-(methylthio)cyclohexanone (330 mg, 1.65 mmol) afforded a mixture of azides **2-138a**, **2-138b**, **2-138c**, and **2-138d** (33 mg, 8%, 58:10:16:16 ratio from ^1H NMR in CDCl_3) after column chromatography (1-3% EtOAc/hexanes). Azides **2-138a**, **2-138b**, **2-138c**, and **2-138d**: R_f = 0.40 (10% EtOAc/hexanes); IR (neat) 2924, 2095, 1697 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{24}\text{H}_{39}\text{N}_4\text{O}_2\text{S}_2$ ($2\text{M}-\text{N}_2+\text{H}$) $^+$ 479.2514, found: 479.2478. Azide **2-138a**: ^1H NMR (500 MHz, CDCl_3) δ 1.41-1.57 (m, 4H), 1.64 (s, 3H), 1.65-1.73 (m, 2H), 1.78-1.93 (m, 3H), 2.03-2.11 (m, 2H), 2.96 (td, J = 15.0, 6.0 Hz, 1H), 3.55 (d, J = 6.6 Hz, 2H), 5.37-5.45 (m, 1H), 5.58-5.67 (m, 1H); ^1H NMR (500 MHz, acetone) δ 1.62-1.72 (m, 4H), 1.772 (s, 3H), 1.80-2.20 (m, 7H), 3.05 (td, J = 14.0, 6.0 Hz, 2H), 3.77 (d, J = 6.6 Hz, 2H), 5.52-5.65 (m, 1H), 5.79-5.90 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.0 (CH_3), 21.0 (CH_2), 26.30 (CH_2), 26.35 (CH_2), 32.6 (CH_2), 36.1 (CH_2), 36.9 (CH_2), 52.8 (CH_2), 56.3 (C), 123.2 (CH_2), 136.5 (CH), 206.6 (C); ^{13}C NMR (125 MHz, acetone) δ 10.9 (CH_3), 21.8 (CH_2), 26.89 (CH_2), 26.90 (CH_2), 33.6 (CH_2), 36.7 (CH_2), 37.5 (CH_2), 53.1 (CH_2), 57.0 (C), 124.2 (CH), 137.4 (CH). Azide **2-138b** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 3.65-3.73 (m, 2H); ^1H NMR (500 MHz, acetone) δ 1.779 (s, 3H), 3.91 (d, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 11.0 (CH_3), 56.4 (C), 122.4 (CH), 135.6 (CH); ^{13}C NMR (125 MHz, acetone) δ 10.9 (CH_3), 56.9 (C), 123.4 (CH), 136.6 (CH). Azides **2-138c** and **2-138d** (diagnostic peaks only): ^1H NMR (500 MHz, CDCl_3) δ 1.62 (s, 3H), 3.65-3.73 (m, 1H), 5.10-5.17 (m, 2H), 5.58-5.67 (m, 1H); ^1H NMR (500 MHz, acetone) δ 1.753 (s, 3H), 1.766 (s, 3H), 3.98-4.06 (m, 1H), 5.28-5.31 (m, 1H), 5.33-5.38 (m, 1H), 5.79-5.90 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 10.94 (CH_3), 10.96 (CH_3), 56.2 (C), 56.3 (C), 65.28 (CH), 65.29 (CH), 118.4 (CH_2), 118.7 (CH_2), 135.5 (CH), 135.6 (CH), 206.64 (C), 206.65 (C); ^{13}C NMR (125 MHz, acetone) δ

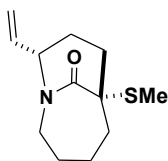
10.79 (CH₃), 10.80 (CH₃), 57.0 (C), 66.03 (CH), 66.07 (CH), 118.5 (CH₂), 118.7 (CH₂), 136.9 (CH), 137.0 (CH).



3-Vinyl-2,3,7,8-tetrahydro-1H-pyrrolo[1,2-a]azepin-5(6H)-one (2-139e).

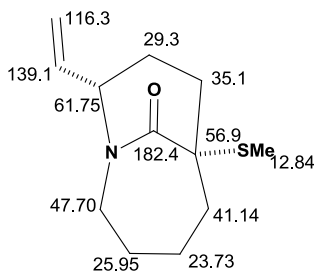
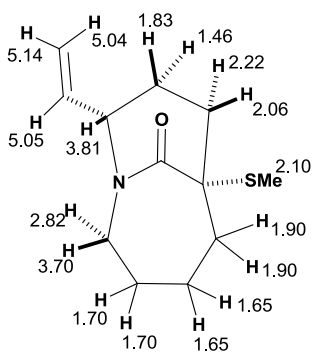
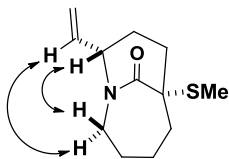
According to the general procedure **VI**, a mixture of azides **2-138a**, **2-138b**, **2-138c**, and **2-138d** (33 mg, 0.13 mmol) and MeAlCl₂ (1 M in hexane, 0.2 mL, 0.2 mmol) in refluxing dichloroethane afforded lactam **2-139e** (2.5 mg, 11%) as a colorless oil and lactam **2-139c** (2 mg, 7%) as a colorless oil after column chromatography (1-30% EtOAc/hexanes). Lactam **2-139e**: *R*_f = 0.35 (50% EtOAc/hexanes); IR (neat) 3367, 2931, 1615, 1405 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₁H₁₅NONa (M+Na)⁺ 200.1051, found: 200.1092; ¹H NMR (500 MHz, acetone) δ 1.49-1.54 (m, 1H), 1.60-1.68 (m, 1H), 1.73-1.83 (m, 2H), 2.03-2.18 (m, 2H), 2.31 (ddd, *J* = 14.7, 10.5, 1.5 Hz, 1H), 2.36-2.52 (m, 3H), 4.67-4.71 (m, 1H), 4.74 (t, *J* = 4.0 Hz, 1H), 4.86-4.93 (m, 2H), 5.68 (ddd, *J* = 17.2, 10.4, 5.1 Hz, 1H); ¹³C NMR (125 MHz, acetone) δ 22.0 (CH₂), 27.8 (CH₂), 29.5 (CH₂), 32.7 (CH₂), 38.6 (CH₂), 61.7 (CH), 104.1 (CH), 113.9 (CH₂), 138.0 (C), 138.8 (CH), 172.0 (C). The following data were used to assign lactam **2-139e**.

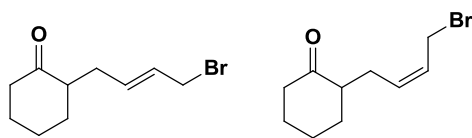




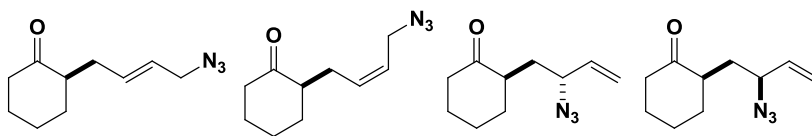
(6*S,9*S**)-6-(Methylthio)-9-vinyl-1-azabicyclo[4.3.1]decan-10-one (2-139c).**

Twisted amide **2-139c**: $R_f = 0.55$ (50% EtOAc); ^1H NMR (500 MHz, CDCl_3) δ 1.43-1.52 (m, 1H), 1.55-1.78 (m, 4H), 1.83-1.88 (m, 1H), 1.89 (dd, $J = 5.0, 6.0$ Hz, 2H), 2.06 (ddd, $J = 6.0, 13.0, 14.0$ Hz, 1H), 2.10 (s, 3H), 2.22 (ddd, $J = 1.8, 6.5, 14.5$ Hz, 1H), 2.82 (td, $J = 5.9, 14.0$ Hz, 1H), 3.67-3.72 (m, 1H), 3.81 (ddd, $J = 2.7, 7.5, 11.5$ Hz, 1H), 5.04 (dd, $J = 0.5, 10.0$ Hz, 1H), 5.14 (d, $J = 17.0$ Hz, 1H), 5.50 (ddd, $J = 7.5, 10.0, 17.5$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 12.8 (CH_3), 23.7 (CH_2), 26.0 (CH_2), 29.3 (CH_2), 35.1 (CH_2), 41.1 (CH_2), 47.7 (CH_2), 56.9 (C), 61.8 (CH), 116.3 (CH_2), 139.1 (CH), 182.4 (C). The following data and NOE correlations were used to assign lactam **2-139c**.



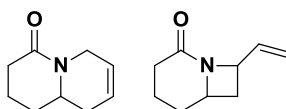


(*E*)-2-(4-Bromobut-2-en-1-yl)cyclohexanone and **(*Z*)-2-(4-bromobut-2-en-1-yl)cyclohexanone**. According to the general procedure **I**, 2-allylcyclohexanone (2.76 g, 20.0 mmol), HG-2 (63 mg, 0.1 mmol) and allyl bromide (3.4 mL, 40 mmol) afforded a mixture of (*E*)-2-(4-bromobut-2-en-1-yl)cyclohexanone and (*Z*)-2-(4-bromobut-2-en-1-yl)cyclohexanone (1.06 g, 23%, 12:1 ratio) as a colorless oil after column chromatography (2-10% EtOAc/hexanes). R_f = 0.50 (10% EtOAc/hexanes); IR (neat): 2935, 1708 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{29}\text{BrO}_2\text{Na}$ ($2\text{M-HBr}+\text{Na}$) $^{+}$ 403.1249, found: 403.1216. *E* isomer: ^1H NMR (400 MHz, CDCl_3) δ 1.35-1.43 (m, 1H), 1.63-1.71 (m, 2H), 1.87-1.92 (m, 1H), 1.99-2.15 (m, 3H), 2.32-2.44 (m, 3H), 2.51-2.57 (m, 1H), 3.94 (d, J = 6.8 Hz, 2H), 5.69-5.80 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.1 (CH_2), 27.9 (CH_2), 32.1 (CH_2), 33.5 (CH_2), 33.7 (CH_2), 42.1 (CH_2), 50.21 (CH), 128.1 (CH), 134.0 (CH), 212.1 (C). *Z* isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.97-4.07 (m, 2H), 5.56-5.62 (m, 1H), 5.69-5.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.2 (CH_2), 26.9 (CH_2), 27.1 (CH_2), 33.8 (CH_2), 42.1 (CH_2), 50.27 (CH), 126.7 (CH), 133.2 (CH), 212.06 (C).



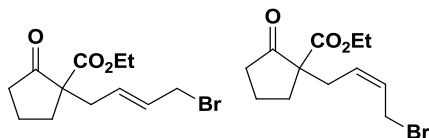
(*R*^{*},*E*)-2-(4-Azidobut-2-en-1-yl)cyclohexanone (2-174a), **(*R*^{*},*Z*)-2-(4-azidobut-2-en-1-yl)cyclohexanone (2-174b)**, **(*R*^{*})-2-((*R*^{*})-2-azidobut-3-en-1-yl)cyclohexanone (2-174c)**, and **(*R*^{*})-2-((*S*^{*})-2-azidobut-3-en-1-yl)cyclohexanone (2-174d)**. According to the general procedure **II**, a mixture of (*E*)-2-(4-bromobut-2-en-1-yl)cyclohexanone and (*Z*)-2-(4-

bromobut-2-en-1-yl)cyclohexanone (1.06 g, 4.6 mmol) afforded a mixture of azides **2-174a**, **2-174b**, **2-174c**, and **2-174d** (740 mg, 84%, 68:14:9:9 from ^1H NMR in CDCl_3) as a colorless oil after column chromatography (1-6% EtOAc/hexanes). Azides **2-174a**, **2-174b**, **2-174c**, and **2-174d**: R_f = 0.45 (20% EtOAc/hexanes); IR (neat): 2936, 2099, 1709 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{31}\text{N}_6\text{O}_2$ ($2\text{M}+\text{H}$) $^+$ 387.2508, found: 387.2502. Azide **2-174a**: ^1H NMR (400 MHz, CDCl_3) δ 1.32-1.43 (m, 1H), 1.63-1.72 (m, 2H), 1.84-1.92 (m, 1H), 2.00-2.15 (m, 3H), 2.28-2.44 (m, 3H), 2.51-2.57 (m, 1H), 3.69 (d, J = 6.4 Hz, 2H), 5.50-5.60 (m, 1H), 5.69-5.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.0 (CH_2), 27.9 (CH_2), 32.2 (CH_2), 33.5 (CH_2), 42.1 (CH_2), 50.3 (CH), 52.7 (CH_2), 124.7 (CH), 134.5 (CH), 212.1 (C). Azide **2-174b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.84 (dd, J = 2.4 Hz, 7.2 Hz, 2H). Azides **2-174c** and **2-174d** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.93-4.02 (m, 1H), 5.22-5.32 (m, 2H), 5.69-5.80 (m, 1H). Azide **2-174b**, **2-174c**, and **2-174d** (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 62.5 (CH), 63.4 (CH), 118.0 (CH_2), 118.6 (CH_2), 123.7 (CH), 133.4 (CH), 135.6 (CH), 135.7 (CH), 211.9 (C), 212.4 (C).



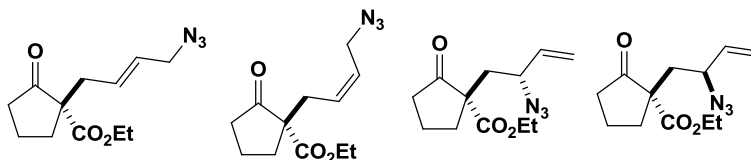
2,3,9,9a-tetrahydro-1H-quinolizin-4(6H)-one (2-175c), and **8-vinyl-1-azabicyclo[4.2.0]octan-2-one (2-175a)**. According to the general procedure **VI**, a mixture of azides **2-174a**, **2-174b**, **2-174c**, and **2-174d** (57 mg, 0.30 mmol) and TiCl_4 (1 M in dichloromethane, 0.45 mL, 0.45 mmol) in refluxing dichloromethane afforded lactam **2-175c** (4 mg, 8%) and lactam **2-175a** (9 mg, 18%, 5:1 ratio) after column chromatography (10-100% EtOAc/hexanes). Lactam **2-175c**: R_f = 0.70 (100% EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 1.60-1.83 (m, 4H), 2.08-2.13 (m, 1H), 2.43-2.50 (m, 1H), 2.53-2.61 (m, 1H), 2.68-2.77 (m,

1H), 3.87-4.09 (m, 3H), 5.85-5.94 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 22.1 (CH₂), 26.4 (CH₂), 30.8 (CH₂), 33.0 (CH₂), 35.8 (CH₂), 41.1 (CH₂), 52.7 (CH), 124.2 (CH), 125.1 (CH), 175.0 (C). Lactam **2-175a** (major isomer): *R_f* = 0.35 (100% EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 1.42-1.52 (m, 1H), 1.67-1.72 (m, 1H), 1.81-1.89 (m, 1H), 1.93 (d, *J* = 13.0 Hz, 1H), 2.0-2.08 (m, 1H), 2.29-2.37 (m, 1H), 2.47 (dd, *J* = 15.3, 6.8 Hz, 1H), 2.53-2.63 (m, 1H), 4.13-4.25 (m, 1H), 4.72 (q, *J* = 6.8 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 6.05 (ddd, *J* = 16.8, 10.3, 6.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.0, 29.8, 36.5, 38.0, 58.4, 60.5, 115.4, 138.0, 175.9. Lactam **2-175a** (minor isomer): *R_f* = 0.45 (100% EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 1.42-1.51 (m, 1H), 1.82-1.88 (m, 1H), 1.91-1.97 (m, 1H), 2.01-2.08 (m, 1H), 2.08-2.14 (m, 1H), 2.16-2.22 (m, 1H), 2.27-2.36 (m, 1H), 2.46 (dd, *J* = 13.9, 7.2 Hz, 1H), 4.23-4.31 (m, 1H), 4.73-4.79 (m, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 5.25 (d, *J* = 17.0 Hz, 1H), 6.04 (ddd, *J* = 16.9, 10.4, 6.0 Hz, 1H).



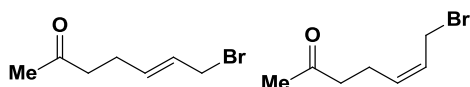
(*E*)-Ethyl 1-(4-bromobut-2-en-1-yl)-2-oxocyclopentanecarboxylate and (*Z*)-ethyl 1-(4-bromobut-2-en-1-yl)-2-oxocyclopentanecarboxylate. A suspension of ethyl 2-oxocyclopentanecarboxylate (3.12 g, 20.0 mmol), potassium carbonate (5.53 g, 40.0 mmol) and (*E*)-1,4-dibromobut-2-ene (4.71 g, 22.0 mmol) in acetone (60 mL) was refluxed for 24 h under N₂ atmosphere. After cooling to room temperature, the reaction was quenched with 1 M HCl (80 mL) to adjust pH = 1; and then extracted with diethyl ether. The combined extracts were washed with saturated sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (1-20% EtOAc/hexanes) to afford a mixture of (*E*)-ethyl 1-(4-bromobut-2-en-1-yl)-2-

oxocyclopentanecarboxylate and (Z)-ethyl 1-(4-bromobut-2-en-1-yl)-2-oxocyclopentanecarboxylate (1.1 g, 39%, 10:1 ratio) as a colorless oil. $R_f = 0.35$ (20% EtOAc/hexanes); IR (neat): 2978, 1748, 1728 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{18}\text{BrO}_3$ ($\text{M}+\text{H}$) $^+$ 289.0439, found: 289.0409; ^1H NMR (400 MHz, CDCl_3) δ 1.20 (t, $J = 7.2$ Hz, 3H), 1.89-2.00 (m, 3H), 2.16-2.24 (m, 1H), 2.28-2.42 (m, 3H), 2.61 (dd, $J = 6.8$ Hz, 14.0 Hz, 1H), 3.86 (d, $J = 7.2$ Hz, 2H), 4.11 (q, $J = 7.2$ Hz, 2H), 5.60-5.75 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1 (CH_3), 19.5 (CH_2), 32.3 (CH_2), 32.4 (CH_2), 35.8 (CH_2), 37.9 (CH_2), 59.8 (C), 61.5 (CH_2), 130.4 (CH), 130.7 (CH), 170.7 (C), 214.3 (C).

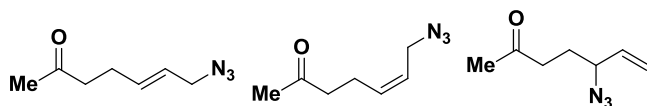


(S^* , E)-Ethyl 1-(4-azidobut-2-en-1-yl)-2-oxocyclopentanecarboxylate (2-170a), (S^* , Z)-ethyl 1-(4-azidobut-2-en-1-yl)-2-oxocyclopentanecarboxylate (2-170b), and (S^*)-ethyl 1-((R^*)-2-azidobut-3-en-1-yl)-2-oxocyclopentanecarboxylate (2-170c). and (S^*)-ethyl 1-((S^*)-2-azidobut-3-en-1-yl)-2-oxocyclopentanecarboxylate (2-170d). According to the general procedure **II**, a mixture of (E)-ethyl 1-(4-bromobut-2-en-1-yl)-2-oxocyclopentanecarboxylate and (Z)-ethyl 1-(4-bromobut-2-en-1-yl)-2-oxocyclopentanecarboxylate afforded a mixture of azides **2-170a**, **2-170b**, **2-170c**, and **2-170d** (850 mg, 89%, 87:10:1.5:1.5 from ^1H NMR in CDCl_3 ; 92:6:1:1 from ^1H NMR in benzene; 92:6:1:1 from ^1H NMR in DMSO) as a colorless oil. Azides **2-170a**, **2-170b**, **2-170c**, and **2-170d**: $R_f = 0.35$ (10% EtOAc/hexanes); IR (neat): 2979, 2100, 1748, 1728, 1228 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{17}\text{N}_3\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 274.1168, found: 274.1131. Azide **2-170a**: ^1H NMR (400 MHz, CDCl_3) δ 1.20 (t, $J = 7.2$ Hz, 3H), 1.85-2.02 (m, 3H), 2.13-2.26 (m, 1H), 2.33-2.44 (m, 3H), 2.66 (dd, $J = 6.0$ Hz, 13.6 Hz, 1H), 3.67 (d, $J = 5.6$ Hz, 2H), 4.13

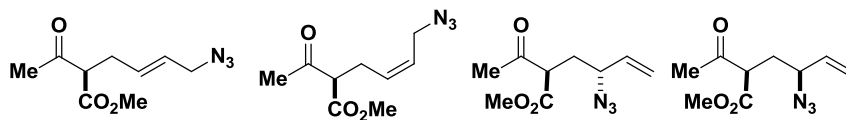
(q, J = 7.2 Hz, 2H), 5.56-5.64 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0 (CH_3), 19.5 (CH_2), 32.2 (CH_2), 36.1 (CH_2), 38.0 (CH_2), 52.4 (CH_2), 59.7 (CH_2), 61.49 (CH_2), 127.4 (CH), 130.7 (CH), 170.7 (C), 214.3 (C). Azide **2-170b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.82 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.6 (CH_2), 31.0 (CH_2), 32.4 (CH_2), 36.5 (CH_2), 47.1 (CH_2), 61.58 (CH_2), 62.7 (C), 126.1 (CH), 129.4 (CH).



(E)-7-Bromohept-5-en-2-one and **(Z)-7-bromohept-5-en-2-one**. According to the general procedure **I**, hex-5-en-2-one (3.92 g, 40.0 mmol), HG-2 (63 mg, 0.1 mmol) and allyl bromide (6.8 mL, 80 mmol) afforded a mixture of (*E*)-7-bromohept-5-en-2-one and (*Z*)-7-bromohept-5-en-2-one (570 mg, 8%, 10:1 ratio) as a colorless oil after column chromatography (1-10% EtOAc/hexanes). R_f = 0.25 (20% EtOAc/hexanes); IR (neat): 2962, 1716 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{29}\text{BrO}_2\text{Na}$ ($2\text{M-HBr}+\text{Na}$) $^+$ 323.0622, found: 323.0620. *E* isomer: ^1H NMR (400 MHz, CDCl_3) δ 2.15 (s, 3H), 2.34 (q, J = 6.8 Hz, 2H), 2.55 (q, J = 6.8 Hz, 2H), 3.93 (d, J = 6.4 Hz, 2H), 5.68-5.80 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.0 (CH_2), 29.98 (CH_3), 33.0 (CH_2), 42.46 (CH_2), 127.3 (CH), 134.4 (CH), 207.5 (C). *Z* isomer (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 2.16 (s, 3H), 2.41 (q, J = 7.2 Hz, 2H), 2.56 (q, J = 7.2 Hz, 2H), 4.02 (d, J = 8.0 Hz, 2H), 5.52-5.59 (m, 1H), 5.68-5.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1 (CH_2), 26.8 (CH_2), 30.01 (CH_3), 42.50 (CH_2), 126.4 (CH), 133.7 (CH), 207.6 (C).

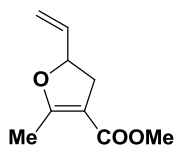


(*E*)-7-Azidohept-5-en-2-one (**2-160a**), (*Z*)-7-azidohept-5-en-2-one (**2-160b**) and 5-azidohept-6-en-2-one (**2-160c**). According to the general procedure **II**, (*E*)-7-bromohept-5-en-2-one and (*Z*)-7-bromohept-5-en-2-one (570 mg, 2.98 mmol) afforded a mixture of azides **2-160a**, **2-160b**, and **2-160c** (367 mg, 81%, 63:7:30 ratio in ^1H NMR acetone; 63:7:30 ratio in ^1H NMR CDCl_3) as a colorless oil after column chromatography (1-10% EtOAc/hexanes). Azides **2-160a**, **2-160b**, and **2-160c**: R_f = 0.50 (20% EtOAc/hexanes); IR (neat): 2927, 2101, 1717 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{23}\text{N}_6\text{O}_2$ ($2\text{M}+\text{H}$) $^+$ 307.1883, found: 307.1858. Azide **2-160a**: ^1H NMR (400 MHz, acetone) δ 2.11 (s, 3H), 2.27-2.38 (m, 2H), 2.55-2.61 (m, 2H), 3.76 (d, J = 6.4 Hz, 2H), 5.50-5.64 (m, 1H), 5.71-5.87 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 26.1 (CH_3), 28.9 (CH_2), 42.2 (CH_2), 52.2 (CH_2), 123.7 (CH), 135.2 (CH), 206.19 (C). Azide **2-160b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.93 (d, J = 7.2 Hz, 2H). Azide **2-160c** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 1.71-1.81 (m, 2H), 2.16 (s, 3H), 2.55-2.61 (m, 2H), 4.01 (q, J = 7.2 Hz, 1H), 5.29-5.36 (m, 2H), 5.71-5.87 (m, 1H). Azide **2-160b**, and **2-160c** (diagnostic peaks only): ^{13}C NMR (100 MHz, acetone) δ 21.4 (CH_3), 27.9 (CH_2), 38.7 (CH_2), 42.3 (CH_2), 46.7 (CH_2), 64.2 (CH), 117.9 (CH_2), 123.0 (CH), 134.5 (CH), 135.8 (CH), 206.23 (C).



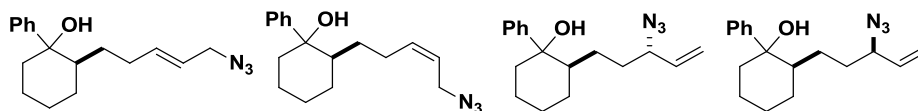
(*R^**,*E*)-Methyl 2-acetyl-6-azidohept-4-enoate (**2-176a**), (*R^**,*Z*)-methyl 2-acetyl-6-azidohept-4-enoate (**2-176b**), (*2R^**,*4R^**)-methyl 2-acetyl-4-azidohept-5-enoate (**2-176c**), and (*2R^**,*4S^**)-methyl 2-acetyl-4-azidohept-5-enoate (**2-176d**). To a solution of methyl 1-

acetyl-2-vinylcyclopropanecarboxylate (504 mg, 3.00 mmol) in dichloromethane (20 mL) under N₂ atmosphere at -78 °C was added titanium tetrachloride (1 M in dichloromethane, 3.6 mL, 3.6 mmol) over 10 min. After 30 min, TMSN₃ (517 mg, 4.5 mmol) was added slowly to the resulting dark-red mixture. It was naturally warmed to room temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride at 0 °C and extracted with dichloromethane. The combined organic extracts were washed with saturated sodium bicarbonate and brine, and then dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (1-7% EtOAc/hexanes) to afford methyl 2-methyl-5-vinyl-4,5-dihydrofuran-3-carboxylate (30 mg, 6%) as a colorless oil and a mixture of azides **2-176a**, **2-176b**, **2-176c**, and **2-176d** (150 mg, 24%, 66:20:7:7 ratio from ¹H NMR in CDCl₃) as a colorless oil. Azides **2-176a**, **2-176b**, **2-176c**, and **2-176d**: *R_f* = 0.25 (20% EtOAc/hexanes); IR (neat): 2956, 2102, 1745, 1716 cm⁻¹; HRMS (ESI) *m/z* calculated for C₉H₁₃N₃O₃Na (M+Na)⁺ 234.0855, found: 234.0880. Azide **2-176a**: ¹H NMR (400 MHz, CDCl₃) δ 2.22 (s, 3H), 2.60 (t, *J* = 7.2 Hz, 2H), 3.53 (t, *J* = 7.2 Hz, 1H), 3.67 (d, *J* = 6.0 Hz, 2H), 3.72 (s, 3H), 5.56-5.69 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 29.2 (CH₃), 30.6 (CH₂), 52.3 (CH or CH₃), 52.5 (CH₂), 59.0 (CH or CH₃), 126.1 (CH), 131.8 (CH), 169.4 (C), 210.9 (C). Azide **2-176b** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 3.95-3.97 (m, 2H). Azides **2-176c** and **2-176d** (diagnostic peaks only): ¹H NMR (400 MHz, CDCl₃) δ 5.27-5.32 (m, 2H), 5.56-5.69 (m, 1H). Azide **2-176b**, **2-176c**, and **2-176d** (diagnostic peaks only): ¹³C NMR (100 MHz, CDCl₃) δ 58.7 (CH), 62.7 (CH), 62.8 (CH), 119.1 (CH₂), 119.2 (CH₂), 129.0 (CH), 130.9 (CH), 134.6 (C), 134.7 (C), 169.4 (C), 201.9 (C).

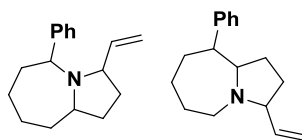


Methyl 2-methyl-5-vinyl-4,5-dihydrofuran-3-carboxylate. $R_f = 0.55$ (20%

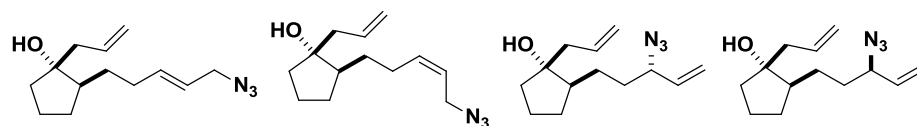
EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 2.19 (s, 3H), 2.65 (dd, $J = 8.0$ Hz, 14.4 Hz, 1H), 3.04 (t, $J = 12.0$ Hz, 1H), 3.69 (s, 3H), 5.02 (dd, $J = 7.6$ Hz, 17.2 Hz, 1H), 5.17-5.30 (m, 2H), 5.87-5.95 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0 (CH_2), 35.5 (CH_3), 50.8 (CH_2), 82.5 (CH_2), 101.4 (C), 116.6 (CH_2), 136.9 (CH), 166.4 (C), 167.8 (C).



(2R)-2-((E)-5-azidopent-3-en-1-yl)-1-phenylcyclohexanol (2-315a), (2R)-2-((Z)-5-azidopent-3-en-1-yl)-1-phenylcyclohexanol (2-315b), (2R)-2-((S)-3-azidopent-4-en-1-yl)-1-phenylcyclohexanol (2-315c), and (2R)-2-((R)-3-azidopent-4-en-1-yl)-1-phenylcyclohexanol (2-315d). To a solution of azides **65a**, **65b**, **65c** and **65d** (220 mg, 1.06 mmol) in THF (6 mL) at -78°C under N_2 atmosphere was added slowly phenyl magnesium bromide (3 M in diethyl ether, 0.53 mL, 1.59 mmol). After 30 min, the reaction was quenched with aqueous saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with brine, and then dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (1-10% EtOAc/hexanes) to afford a mixture of azides **2-315a**, **2-315b**, **2-315c** and **2-315d** (161 mg, 53%, ratio not determined) as a colorless oil.

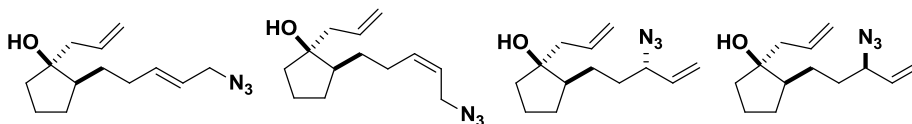


5-Phenyl-3-vinyloctahydro-1H-pyrrolo[1,2-a]azepine (2-316a) and **9-phenyl-3-vinyloctahydro-1H-pyrrolo[1,2-a]azepine (2-316b)**. To a solution of azides **2-315a**, **2-315b**, **2-315c** and **2-315d** (66 mg, 0.23 mmol) in benzene (4 mL) at room temperature under N₂ atmosphere was slowly added tin tetrachloride (1 M in dichloromethane, 0.51 mL, 0.51 mmol). After 15 h, the reaction was cooled to 0 °C, and followed by the slow addition of a solution of sodium borohydride (35 mg, 0.93 mmol) in methanol (3 mL). After 9 h, the reaction was quenched with aqueous NaOH (2 M), extracted with ethyl acetate. The combined organic extracts were washed with brine, and dried over anhydrous sodium sulfate. The concentrated residue was purified by column chromatography (1-15% EtOAc/hexanes) to afford a mixture of amines **2-316a** and **2-316b** (24 mg, 43%) as a colorless oil.



(1R*,2R*)-1-Allyl-2-((E)-5-azidopent-3-en-1-yl)cyclopentanol (2-152a), **(1R*,2R*)-1-allyl-2-((Z)-5-azidopent-3-en-1-yl)cyclopentanol (2-152b)**, **(1R*,2R*)-1-allyl-2-((S*)-3-azidopent-4-en-1-yl)cyclopentanol (2-152c)**, and **(1R*,2R*)-1-allyl-2-((R*)-3-azidopent-4-en-1-yl)cyclopentanol (2-152d)**. To a solution of azides **2-148** (350 mg, 1.81 mmol) in THF (10 mL) under N₂ atmosphere was added anhydrous CeCl₃ (534 mg, 2.17 mmol). After 1 h at room temperature, the mixture was cooled to 0 °C and allyl magnesium bromide (1 M in diethyl ether, 2.2 mL, 2.2 mmol) was slowly added. After 1 h, the reaction was quenched with 20% aqueous acetic acid (20 mL) and extracted with ethyl acetate. The

combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, then dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (1-5% EtOAc/hexanes) to afford a mixture of azides **2-152a**, **2-152b**, **2-152c** and **2-152d** (65 mg, 15%, 62:8:15:15 ratio from ^1H NMR in acetone) as a colorless oil, a mixture of azides **2-162a**, **2-162b**, **2-162c** and **2-162d** (181 mg, 43%, 64:8:14:14 ratio from ^1H NMR in acetone) as a colorless oil, and recovered azide **2-148** (104 mg). Azides **2-152a**, **2-152b**, **2-152c** and **2-152d** (62:8:15:15 ratio): R_f = 0.30 (20% EtOAc/hexanes); IR (neat): 3445, 2945, 2098, 1243 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{26}\text{H}_{43}\text{N}_4\text{O}_2$ ($2\text{M-N}_2+\text{H}$) $^+$ 443.3386, found: 443.3398. Azide **2-152a**: ^1H NMR (400 MHz, acetone) δ 1.11-1.21 (m, 1H), 1.23-1.34 (m, 1H), 1.47-1.85 (m, 5H), 1.94-2.32 (m, 6H), 3.77 (d, J = 6.4 Hz, 2H), 5.03-5.09 (m, 2H), 5.57-5.63 (m, 1H), 5.79-5.89 (m, 1H), 5.96-6.06 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.1 (CH_2), 28.1 (CH_2), 29.3 (CH_2), 31.0 (CH_2), 37.2 (CH_2), 39.9 (CH_2), 49.7 (CH), 52.4 (CH_2), 81.1 (C), 116.2 (CH_2), 123.1 (CH), 135.6 (CH), 136.8 (CH). Azide **2-152b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.90 (d, J = 7.2 Hz, 2H). Azides **2-152c** and **2-152d** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.98 (q, J = 6.8 Hz, 1H), 5.03-5.09 (m, 2H), 5.27-5.36 (m, 2H), 5.79-5.89 (m, 1H), 5.96-6.06 (m, 1H). Azides **2-152b**, **2-152c** and **2-152d** (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 65.1 (CH), 65.2 (CH), 80.4 (C), 80.5 (C), 117.3 (CH_2), 117.4 (CH_2).



(1*S**,2*R**)-1-Allyl-2-((*E*)-5-azidopent-3-en-1-yl)cyclopentanol (2-162a),
 (1*S**,2*R**)-1-allyl-2-((*Z*)-5-azidopent-3-en-1-yl)cyclopentanol (2-162b), (1*S**,2*R**)-1-allyl-
 2-((*S**)-3-azidopent-4-en-1-yl)cyclopentanol (2-162c), and (1*S**,2*R**)-1-allyl-2-((*R**)-3-

azidopent-4-en-1-yl)cyclopentanol (2-162d). Azide **2-162a**, **2-162b**, **2-162c** and **2-162d** (64:8:14:14 ratio from ^1H NMR in acetone): $R_f = 0.25$ (20% EtOAc/hexanes); IR (neat): 3473, 2939, 2098 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{26}\text{H}_{43}\text{N}_4\text{O}_2$ ($2\text{M}-\text{N}_2+\text{H}$) $^+$ 443.3386, found: 443.3353. Azide **2-162a**: ^1H NMR (400 MHz, acetone) δ 1.35-1.78 (m, 9H), 1.82-1.90 (m, 1H), 2.01-2.10 (m, 1H), 2.15-2.21 (m, 1H), 2.41 (dd, $J = 6.8$ Hz, 13.6 Hz, 2H), 3.77 (d, $J = 6.4$ Hz, 2H), 5.01-5.08 (m, 2H), 5.56-5.63 (m, 1H), 5.77-5.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8 (CH_2), 28.1 (CH_2), 29.7 (CH_2), 31.0 (CH_2), 38.5 (CH_2), 44.0 (CH_2), 47.0 (CH), 52.4 (CH_2), 80.5 (C), 116.3 (CH_2), 122.9 (CH), 135.5 (CH), 137.1 (CH). Azide **2-162b** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.90 (d, $J = 7.2$ Hz, 2H). Azide **2-162c** and **2-162d** (diagnostic peaks only): ^1H NMR (400 MHz, acetone) δ 3.97 (q, $J = 6.8$ Hz, 1H), 5.01-5.08 (m, 2H), 5.27-5.36 (m, 2H), 5.77-5.98 (m, 2H). Azide **2-162b**, **2-162c** and **2-162d** (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 49.7 (CH), 65.2 (CH), 65.4 (CH), 80.5 (C), 81.1 (C), 116.2 (CH_2), 116.4 (CH_2), 117.2 (CH_2), 117.5 (CH_2), 122.0 (CH), 123.1 (CH), 135.5 (CH), 136.0 (CH), 136.4 (CH), 136.8 (CH).

CHAPTER 3

TOTAL SYNTHESIS OF ALKALOID 205B

3.1 Introduction

Tricyclic alkaloids have attracted considerable attention from synthetic and medicinal chemists due to their synthetically challenging skeletons and interesting biological activities (Figure 106). The most well-known class of tricyclic alkaloids has a 2-methyl-perhydro-9b-azaphenalene skeleton, and includes propyleine, precoccineline, hippodamine, and myrrhine. Alkaloid **205B**, with a unique tricyclic 8b-azaacenaphthylene ring system, was isolated from skin extracts of the Panamanian poisonous frog *Dendrobates pumilio*, and characterized in 1987 by Daly and coworkers.¹¹⁵ A year later, its structure was re-assigned by the same group.¹¹⁶ Alkaloid (+)-**205B** was reported to selectively block the $\alpha 7$ nAChR over $\alpha 4\beta 2$ and $\alpha 3\beta 4$ receptors with modest potency.¹¹⁷ In addition, 0.9 mg of the related alkaloids **261C** and **263G** were also isolated by the same group from skin extracts of a Madagascan poison frog *Mantella betsileo* in 2003.¹¹⁸

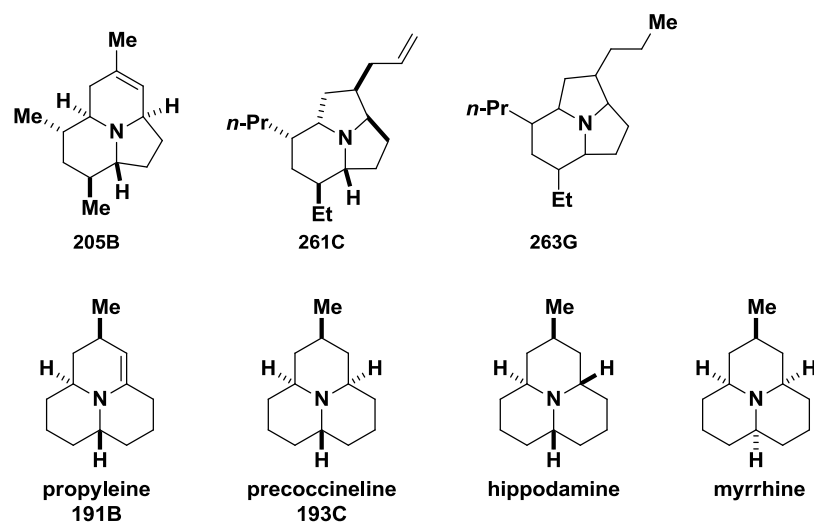
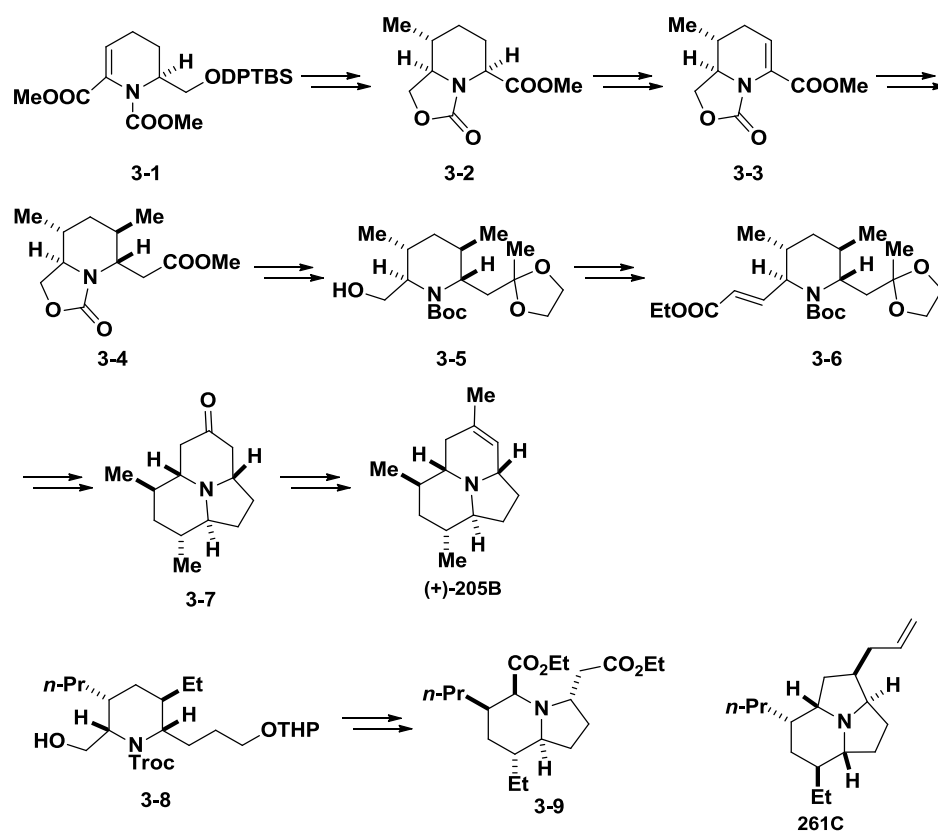


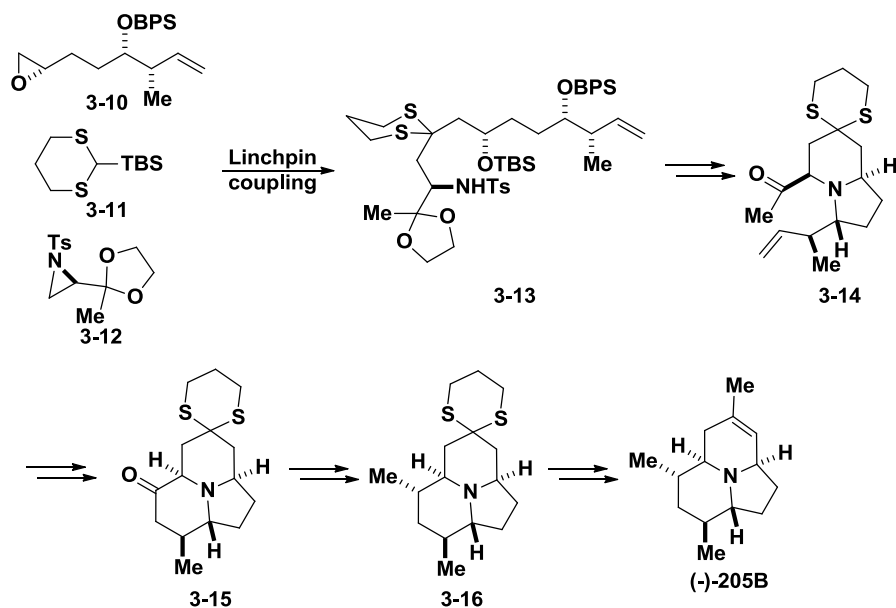
Figure 106. Tricyclic alkaloids.

Four total syntheses of alkaloid **205B** have been reported to date. The first was reported by Toyooka and coworkers (Scheme 74).^{119,120} It used a pair of double asymmetric conjugate additions to establish the trans 1,3-dimethyl groups of **3-4**, followed by an imine-mediated aldol reaction to construct tricyclic ring system **3-7**. Further transformations completed the total synthesis in an overall 1.6% yield over 35 steps from commercial starting materials. A similar strategy was also used in an attempted synthesis of alkaloid **261C**.¹²⁰ However, only the synthesis of **3-9**, an advanced intermediate toward **261C**, has been reported so far.



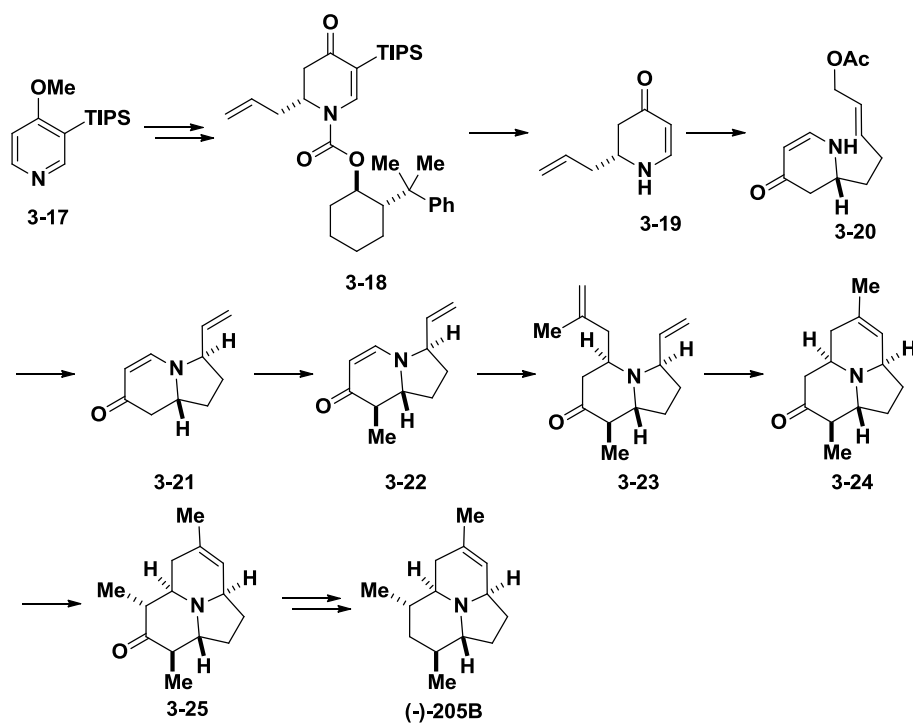
Scheme 74. The first total synthesis by Toyooka and coworkers.

The second total synthesis of (-)-205B was reported by Smith and coworkers (Scheme 74),^{121,122} in which the construction of the indolizine ring system **3-14** was achieved by the dithiane-mediated coupling and Mitsunobu reaction. A cross-metathesis reaction finished the construction of tricyclic ring system **3-15**, and further modifications completed the total synthesis in an overall yield of 5.8% over 23 steps from commercial starting materials.



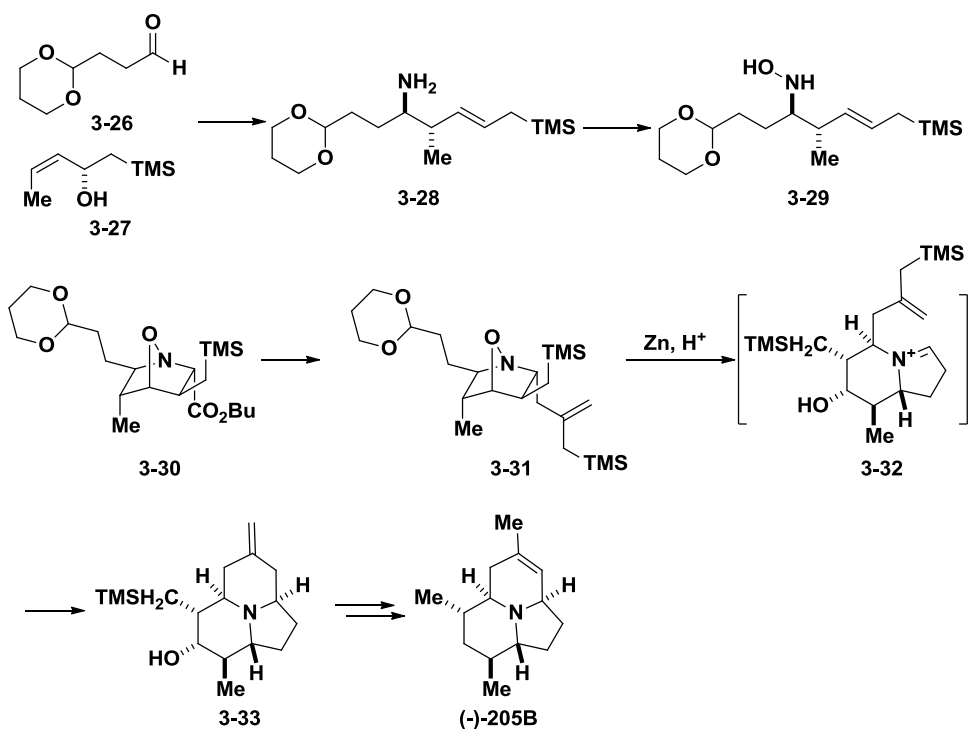
Scheme 75. The second total synthesis by Smith and coworkers.

Comins and coworkers reported another total synthesis of alkaloid (-)-205B in 2011 (Scheme 76).¹²³ It started from an allyl substituted dihydropyrididone **3-19**, cross-metathesis and palladium-mediated cyclization of this material afforded the indolidine ring system **3-21**. The subsequent incorporation of methyl group and allyl group led to the cross-metathesis precursor **3-23**. Following the cross-metathesis, removal of carbonyl group accomplished the total synthesis in 11 steps in an 8% overall yield.



Scheme 76. The third total synthesis by Comins and coworkers.

Micalizio and coworkers reported their total synthesis of alkaloid **205B** in 2012 through two stereoselective synthetic steps: titanium-mediated allylic imine cross-coupling reaction and a nitron-involved [3+2] cycloaddition (Scheme 77).^{124,125} The final ring-closure was achieved by an allylsilane cyclization.



Scheme 77. The fourth total synthesis by Micalizio and coworkers.

3.2 Retrosynthetic analysis

With the combination of allylic azide rearrangement and the intramolecular Schmidt reaction in hand, we sought to apply this newly-developed methodology to the total synthesis of alkaloid **205B**. Our synthetic route started with the diastereoselective synthesis of bicyclic lactam **3-36** (Figure 107). Subsequent methylation and reductive allylation of amide could provide the cross-metathesis precursor **3-34**.

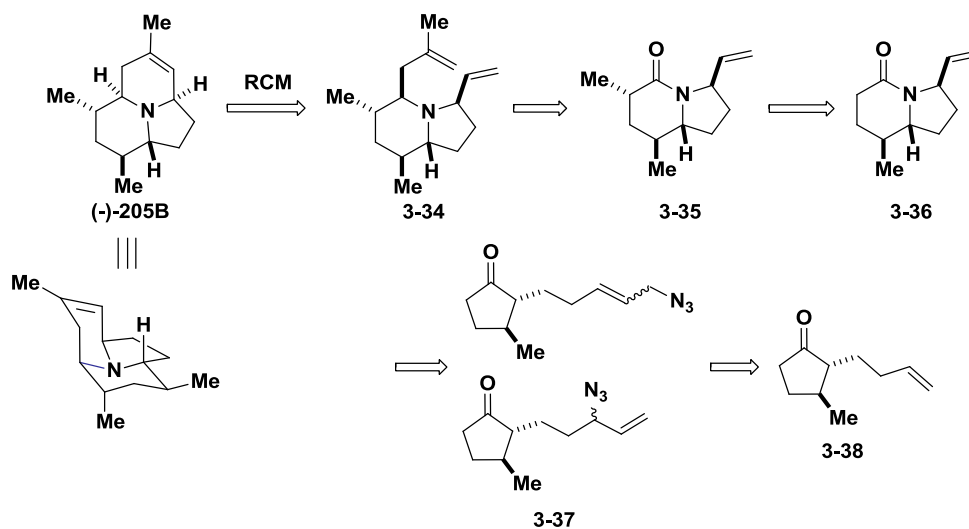


Figure 107. Retrosynthetic analysis of **205B**.

The total synthesis of alkaloid **261C** could also be achieved by a similar strategy starting from 2-(but-3-en-1-yl)-3-ethylcyclopentanone **3-40** (Figure 108). Furthermore, this synthetic route could provide more isomers of **261C** to confirm if wrong stereochemistry was assigned to natural isomer of alkaloid **261C**.

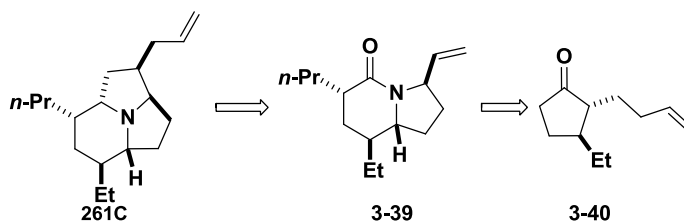


Figure 108. Retrosynthetic analysis of **261C**.

3.3 Preparation of 2-(but-3-en-1-yl)-3-methylcyclopentanone

For the preparation of *trans*-2-(but-3-en-1-yl)-3-alkylcyclopentanone (**3-38** and **3-40**), the first methodology considered was the conjugate addition of an alkyl cuprate to cyclopentenone, followed by trapping of the *in situ* generated anion with 4-iodo-1-butene

(Figure 109). Such conjugate additions have been reported in both racemic and enantioselective fashions.^{126,127}

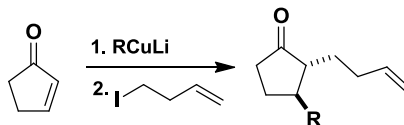
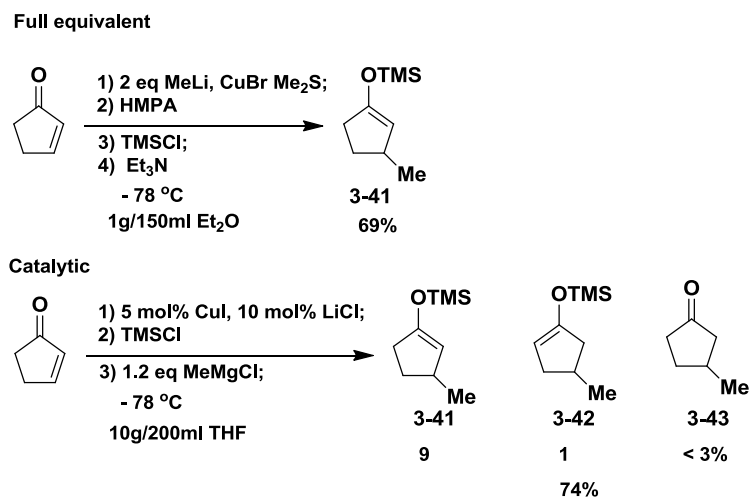


Figure 109. Synthesis of 2-(but-3-en-1-yl)-3-alkylcyclopentanone.

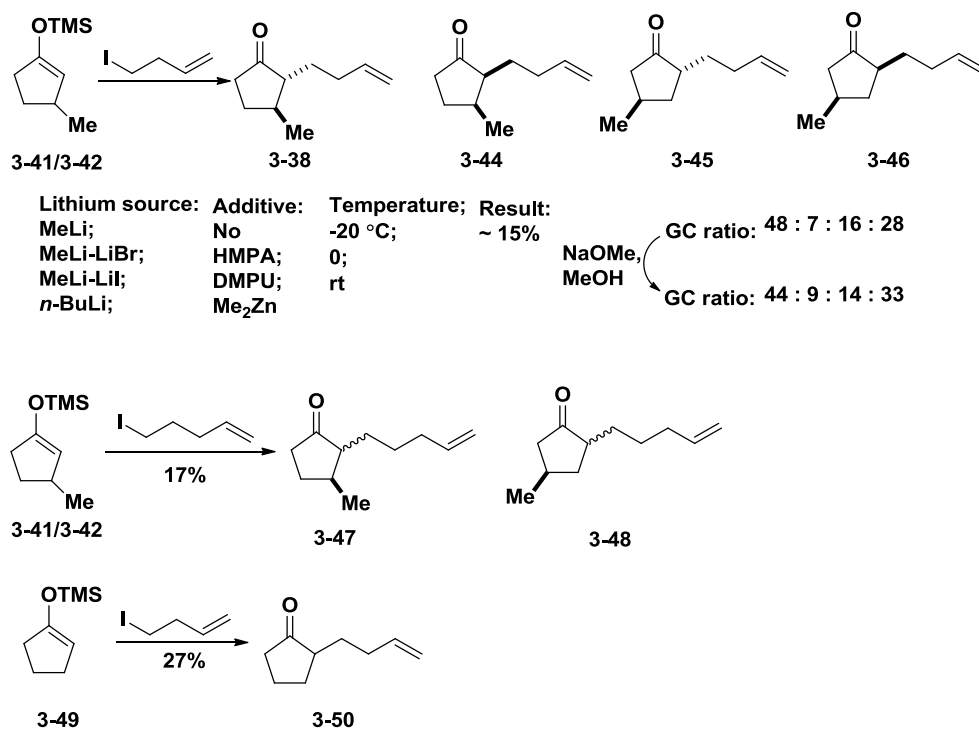
However, 4-iodo-1-butene, unlike methyl iodide, benzyl iodide, and aldehyde, was not considered as a good electrophile.¹²⁸ Two-step procedure can be an alternative route to 2,3-dialkylated cyclopentanone. First, TMSCl is used to trap the anion generated from the conjugated addition of alkyl cuprate to cyclopentenone. In the second step, the formed TMS enol ether is treated with methyl lithium, and thus the generated enolate reacts with electrophile to afford the desired ketone.

A TMS enol ether can be prepared by two methods (Scheme 78). One is to use one equivalent of methyl cuprate and the other is to use methyl Grignard reagent with a catalytic amount of copper iodide.¹²⁹ Both methods were attempted and each was found to have advantages and disadvantages. Pure product was obtained from cuprate reaction, but scale-up was problematic. The second could be scaled up, but the product was contaminated with one regioisomer and the methylated ketone **3-43**, which resulted from the hydrolysis of TMS enol ether.



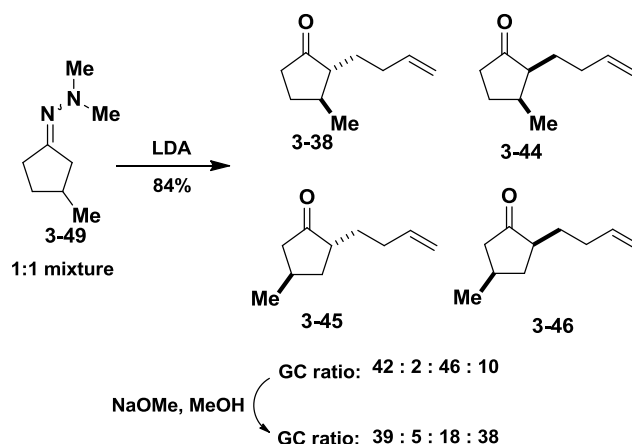
Scheme 78. Preparation of TMS enol ether.

Many attempts were made to get desired ketone **3-38** from enol ether **3-41**, such as trying different base sources, e.g. *n*-BuLi, MeLi, MeLi-LiBr, and MeLi-LiI, different additives and various temperatures (Scheme 79). Unfortunately, no satisfactory results were obtained. The best result obtained so far was a 15% yield of four inseparable isomers **3-38**, **3-44**, **3-45**, and **3-46**. When the products were treated with base in order to increase the ratio of desired **3-38**, the ratio of mixtures remained similar, signaling that the alkylated products were obtained as their thermodynamic products. There are several possibilities for these results. The elimination of 4-iodo-1-butene is one of them because volatile butadiene may be generated under strong basic condition. However, a similar yield was obtained when using 5-iodo-1-pentene, suggesting that the elimination of 4-iodo-1-butene was not a major contribution to the low yield. Although the steric hindrance of 3-methyl group in the cyclopentane ring system may block the alkylation, only a little better yield was obtained in our hands when (cyclopent-1-en-1-yloxy)trimethylsilane was used for this alkylation.



Scheme 79. Preparation of alkylated ketones.

At that time, we didn't have good explanations for the formation of four regioisomers. Thus they were alternatively prepared by alkylation of hydrazone **3-49** and hydrolysis of alkylated hydrazone (Scheme 80). It's interesting that the ratio of four isomers changed dramatically after the treatment of base, which suggested that the products obtained from alkylation are kinetic products while the equilibrated products are thermodynamic ones.



Scheme 80. Alkylation route to ketone **3-38**.

The rationale for this phenomenon was proposed in Figure 110 and Figure 111. There are two enolates formed during the reaction, 2-enolate and 5-enolate, either during the attack of methyl lithium to TMS enol ether or the deprotonation of hydrazone. Two attacking models exist for each enolate, in which methyl group of the most stable conformation is located at the pseudo-equatorial positions. For 2-enolate, pathway *a* is favored over pathway *b* due to the steric hindrance of H₃ in the puckered methylene carbon, suggesting that 2,3-trans isomer (exo-alkylation) is favored than 2,3-cis isomer (endo-alkylation). Another possible explanation is the competition between the effect of 2-pseudo-axial hydrogen and 2-pseudo-equatorial methyl group on the alkylation. Although H₁ of 2-enolate is at pseudo-axial position, the pseudo-equatorial methyl group occupies much bigger space than the small hydrogen, and this difference may contribute to the formation of 2,3-trans as the major product.

A similar hindrance exists for 5-enolate. But in this case, pathway *b* is favored over pathway *a* due to the big difference between pseudo-axial H₁ and pseudo-equatorial H₂. In such a scenario, 2,4-trans was produced as the major isomer. However, the existence of pseudo-axial H₃ can compromise the contribution of endo-alkylation to some extent, which

may explain why the kinetic ratio of **3-45** and **3-46** (46:10) is lower than that of **3-38** and **3-44** (44:2).

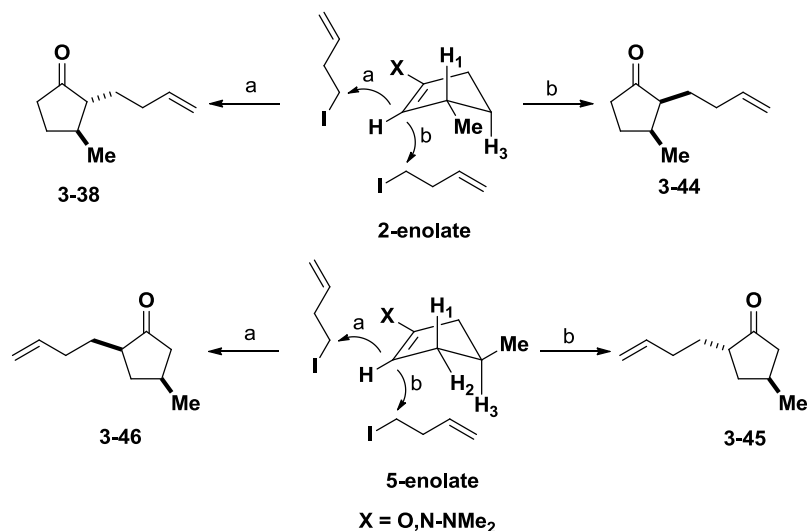


Figure 110. The model for the alkylation of enolate.

Cyclopentane has two stable conformations: envelope and half-chair. However, the difference between them is slight, with the envelope form being the more stable by 0.5 kcal/mol.¹³⁰ Due to the low flipping barrier, it is not surprising that cyclopentane is in a rapid conversion among different intermediate conformations. However, it is not true for substituted cyclopentane. For example, the barrier is 3.40 kcal/mol for methylcyclopentane, in which the most stable conformation (by 0.9 kcal/mol over other conformers) is with the methyl group at the flap of the envelope.¹³⁰ The preferred conformation of cyclopentanone, by 2.4 kcal/mol, is the half-chair with the carbonyl group in the least puckered region with 1.15 kcal/mol of the inter-conversion barrier.¹³⁰

There are four possible stable conformations for substituted cyclopentanone: **A**, **B**, **C**, and **D** (Figure 111). By comparison, **3-38A**, **3-38B**, **3-46A**, and **3-46B** have their both substituents on the pseudo-equatorial positions, and thus **3-38** and **3-46**, the latter being

confirmed in the dynamic kinetic resolution,¹³¹ are the expected thermodynamic products.

The experimental ratio of **3-38** over **3-44** is 39:5, and it is 38:18 for **3-46** and **3-45**.

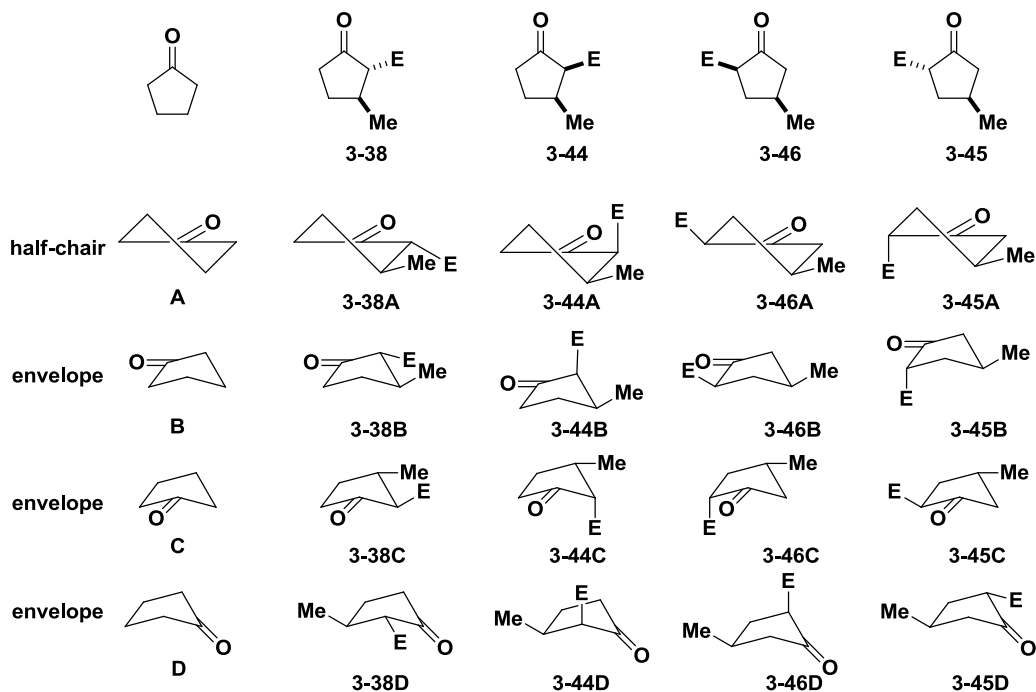


Figure 111. Schematic presentation of cyclopentanone conformations.

Based on the above kinetic and thermodynamic analysis, all the ketones should be identified in the spectra. First, all the spectra were compared for ketones obtained from hydrazone method before with those after the equilibria were reached (Figure 112). The diagnostic peaks were tentatively assigned for each regioisomer, based on the aforementioned kinetic and thermodynamic analysis (Figure 113). Theoretically, four regioisomers of ketone would give eight peaks in the GC chromatogram while chiral GC column is used; however, some peaks may be overlapped or overlay, and then only six peaks were shown, the identity of which will be analyzed later in this chapter.

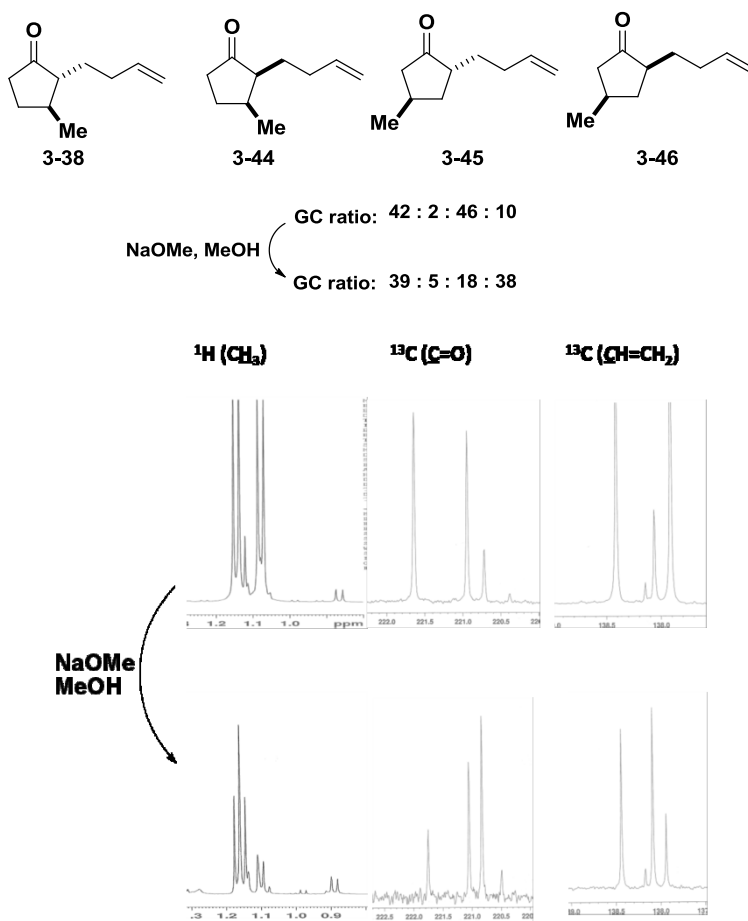


Figure 112. Spectral comparison before and after basic equilibration.

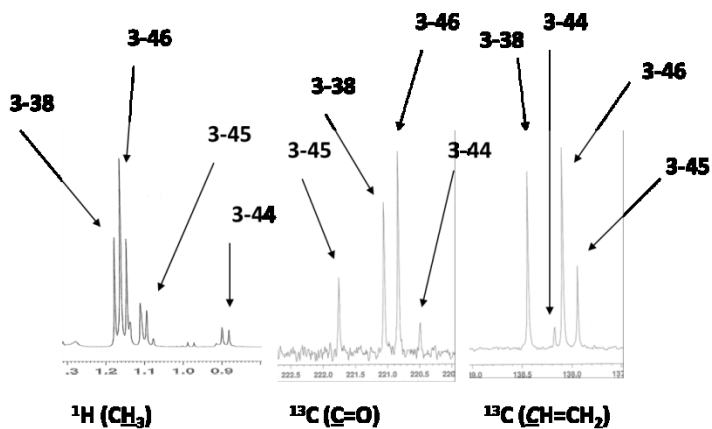
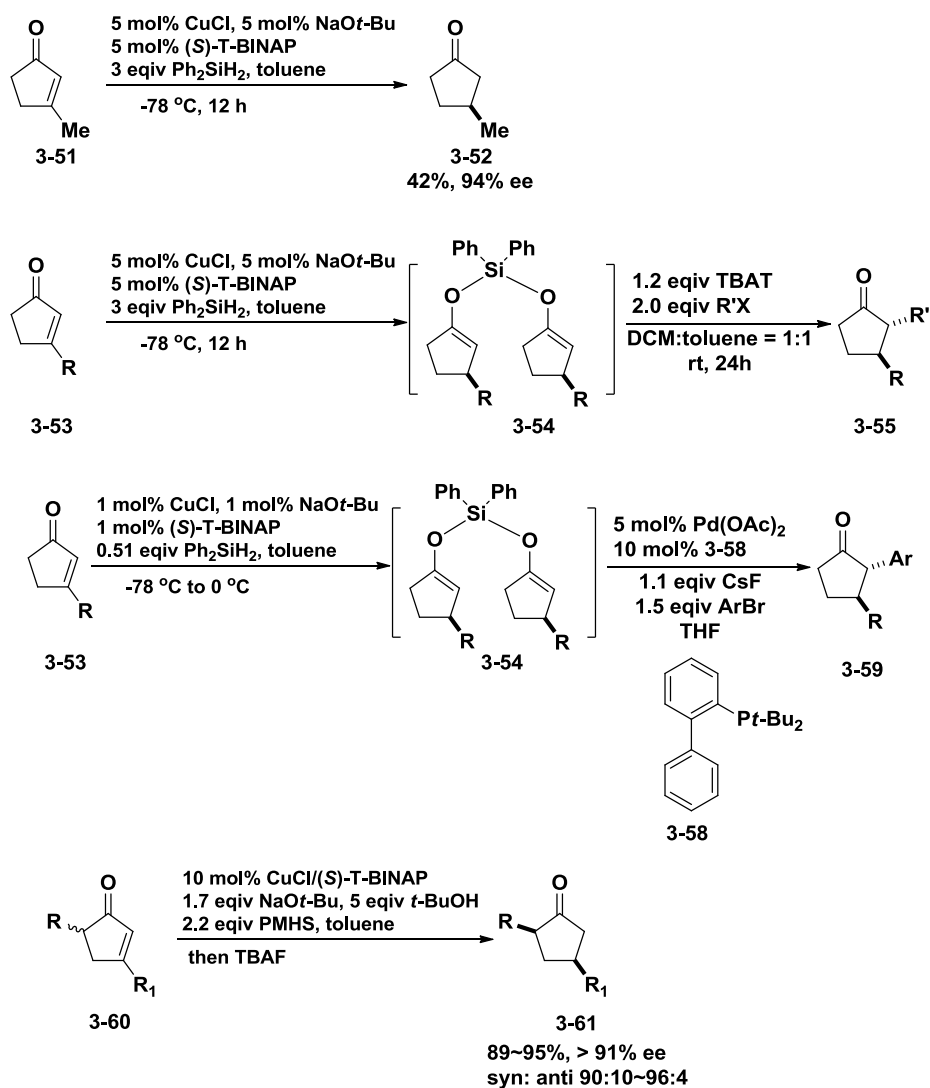


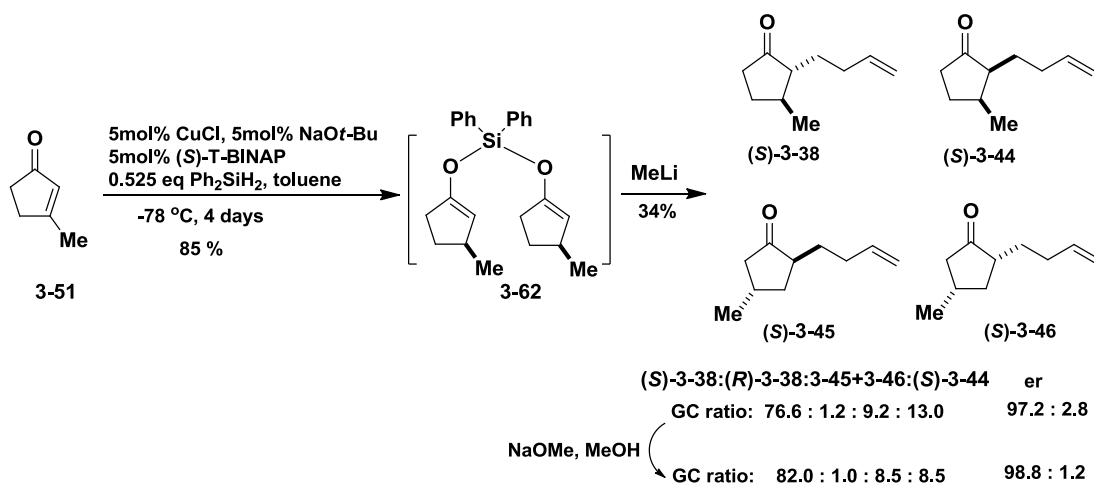
Figure 113. Assignment for regioisomers.

Preparation of enantiopure ketone 3-38. Asymmetric conjugate addition has been extensively studied, and numerous catalysts have been developed to achieve high enantioselectivity for substituted cyclohexenones, but not for cyclopentenones.¹³² Unsubstituted cyclopentenone was referred as “a special case” due to the flatness of this molecule, whose both faces are difficult to be differentiated by chiral catalysts.¹²⁷ As an alternative method, asymmetric conjugate reduction has been developed for the preparation of the enantiopure ketones. Buchwald and coworkers reported a series of seminal studies using Cu-H catalyst.^{131,133-135} This methodology has been combined with other reactions, such as alkylations or arylation,^{17,134,135} and dynamic kinetic resolution.¹³¹ The dynamic kinetic resolution also confirmed that 2,4-cis cyclopentanone is more stable than 2,4-trans isomer.



Scheme 81. Buchwald's asymmetric conjugate reduction and his applications.

Following the preparation of silane diol intermediate **3-62**, several alkylation conditions, similar to what described in Scheme 79, were tested in order to prepare ketone **3-38** (Scheme 82). Only 34% yield was obtained for four regioisomers with less undesired regioisomers **3-45** and **3-46** (<10%), and high enantioselectivity of **3-38** (~95% ee).



Scheme 82. Preparation of enantiopure ketone **3-38**.

A similar equilibration, which was described in Scheme 80, was carried out for this enantiopure mixture of ketones. All the GC chromatograms were compared before and after equilibria of racemic and enantiopure ketones (Figure 114 and Figure 115). In theory, each isomer should present two identical peaks in the GC chromatogram while chiral GC column is used. The first and second peaks (from the left) always have the same percentage in different batches of alkylation, and even the equilibrations. Combined with NMR results, they are tentatively assigned as **(S)-3-38** and **(R)-3-38**, and the first peak is assigned as the *(S)*-isomer, based on the reported enantioselective conjugate reduction. Following a similar strategy, the rest peaks were correspondingly assigned (Figure 116).

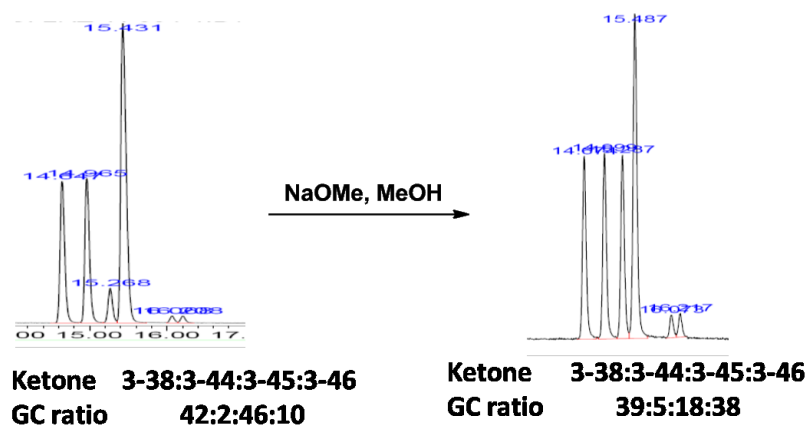


Figure 114. GC chromatograms of racemic ketones.

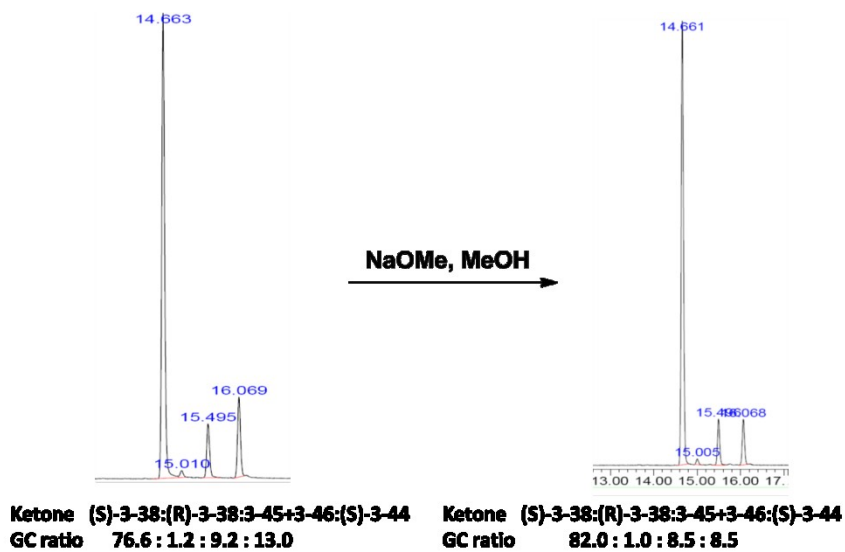


Figure 115. GC chromatograms of enantiopure ketones.

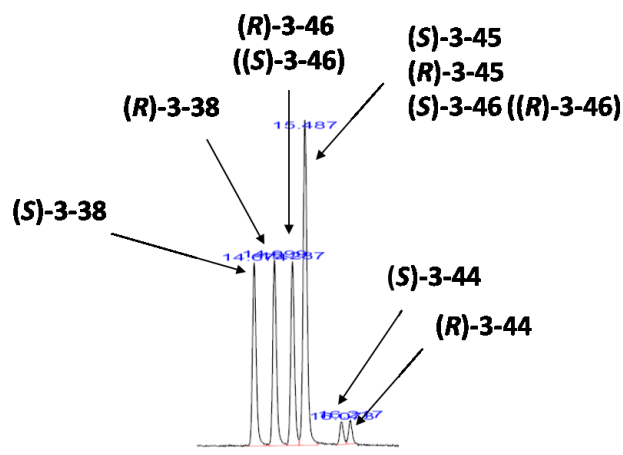
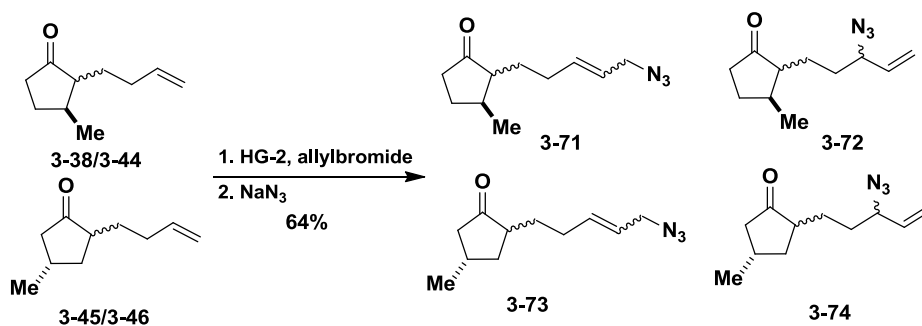


Figure 116. Peak assignment of GC chromatogram.

3.4 Synthetic studies toward alkaloid 205B

Although pure ketone **3-38** was prepared, studies directed forward advancing the mixture of ketones to alkaloid **205B** were carried out in the hope that the desired isomer could be singled out in a subsequent step. Doing so would also help to find appropriate conditions for later conversions and accordingly save time to screen conditions after pure ketone **3-38** is obtained.

A mixture of allylic azide was obtained in 64% yield following the one-pot procedure developed in the Chapter 2 (Scheme 83). The ratio of these mixtures could not be determined using NMR techniques due to the many possible isomers present.



Scheme 83. Preparation of allylic azides.

Based on the decarboxylative allylation by Tunge and others,¹³⁶ an alternative preparation of allylic azides **3-86** and **3-87** was proposed via palladium-facilitated azidation (Figure 117). Two competing pathways could occur upon treatment with Pd catalysts. In one, an azide source could react with intermediate **3-85** to give a set of allylic azides, and in the other, the intramolecular alkylation of **3-85** might occur to afford spirobicyclic ketones **3-88** and **3-89**.

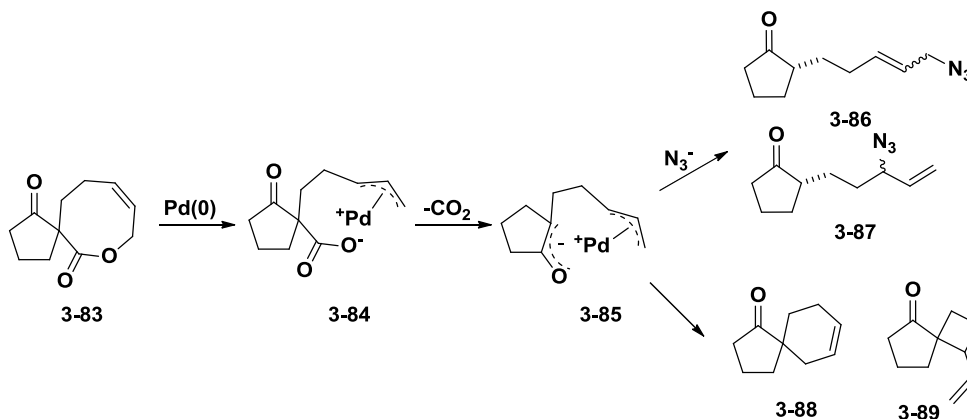
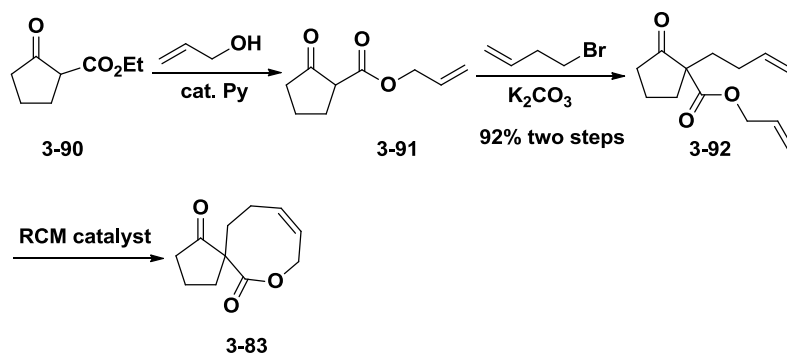


Figure 117. Pd(0)-facilitated decarboxylative preparation of allylic azides.

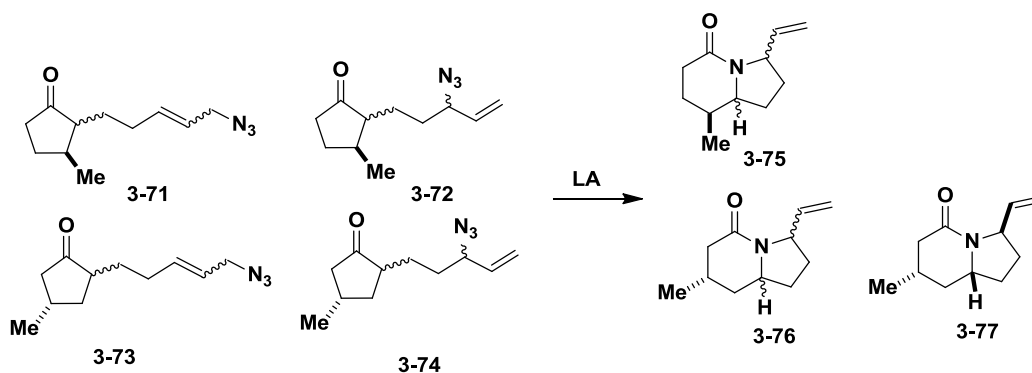
For the preparation of **3-83**, ethyl ester **3-90** was converted to allyl ester **3-91** (Scheme 84). Alkylation afforded the intramolecular cross-metathesis precursor **3-92**. However, all the tested conditions failed to afford **3-83**. More different catalysts will be tested for this conversion.



Scheme 84. Preparation of ketone **3-83**.

Various conditions for the combination of allylic azide rearrangement and intramolecular Schmidt reaction have been screened. TiCl_4 afforded the best yield in 68% yield of a mixture of **3-75** and **3-76**, and 4% of pure **3-77** (Table 40). The relative stereochemistry of **3-77** was assigned based on the 2D NMR.

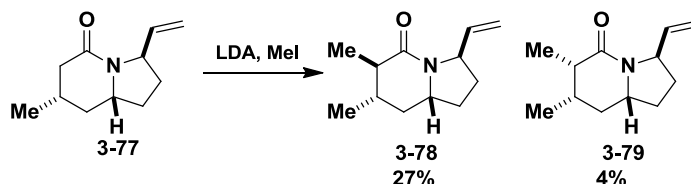
Table 40. Allylic azide rearrangement/intramolecular Schmidt reaction condition screening.



Conditions		Yield (3-77)	Yield (3-75 + 3-76)
1	1.5 eq SnCl_4 , DCM, reflux		15%
2	5 eq TiCl_4 , rt, reflux	7%	30%
3	5 eq TiCl_4 , DCM reflux	9%	39%
4	5 eq TiCl_4 , DCE, reflux	9%	61%

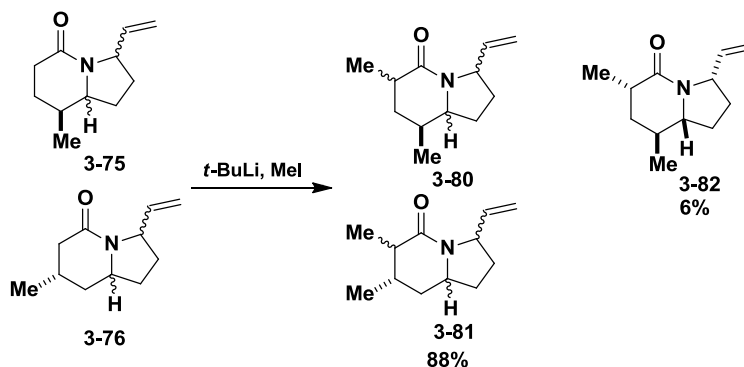
5	5 eq TiCl ₄ , CHCl ₃ , reflux	9%	58%
6	1.5 eq TiCl ₄ , DCE, reflux (1.1 g)	4%	68%

The LDA-mediated methylation was first tested on amide **3-77** with a scale of 13 mg (Scheme 85), and two products with 7:1 ratio were afforded. Their relative stereochemistry was assigned based on 2D NMR. However, this reaction could not be reproduced following further attempts.



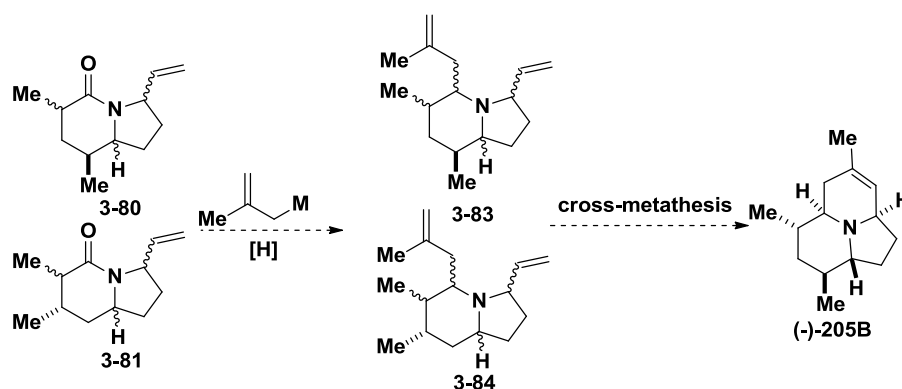
Scheme 85. LDA-assisted methylation.

Because limited amount of **3-77** retarded the further testing, additional conditions for the methylation of amides **3-75** and **3-76** were screened, and the best result was obtained from the treatment with *t*-BuLi followed by methylation, which gave a total 94% yield (Scheme 86). One of the methylated isomers **3-82** was isolated; its relative stereochemistry was assigned by 2D NMR.



Scheme 86. *t*-BuLi assisted methylation.

The next reductive allylation of amide **3-80** and **3-81** could give a mixture of amine **3-83** and **3-84** (Scheme 87). The stereochemistry of this reaction could be controlled by either methyl group or bridgehead hydrogen atom. Alkaloid **205B** could be obtained after the cross-metathesis reaction.



Scheme 87. Reductive allylation of amide.

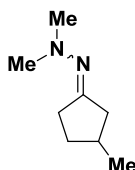
3.5 Conclusion

In this chapter, the synthetic studies towards alkaloid **205B**, which utilized the combination of allylic azide rearrangement and intramolecular Schmidt reaction, were presented.

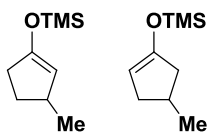
Three methods, enol ether-alkylation, hydrazone-alkylation, and conjugate reduction-alkylation, have been tried to prepare *trans*-2-(but-3-en-1-yl)-3-alkylcyclopentanone, which is a key intermediate in the syntheses of alkaloids **205B** and **261C**. These methods afforded a mixture of four regioisomeric ketones with different ratios. Their results were analyzed from kinetic and dynamic perspectives and their diagnostic peaks on the ¹H, ¹³C NMR and GC were assigned. An alternative route to prepare enantiopure ketone **3-38** from pulegone was proposed.

The mixture of ketones was pushed forwards to screen the conditions for next conversions to alkaloid **205B**. Two pure isomers were separated in the combination and methylation step respectively. The reductive alkylation of amide is in progress. The decarboxylative allylation was proposed for the preparation of allylic azides.

3.6 Experimental data



1,1-Dimethyl-2-(3-methylcyclopentylidene)hydrazine (3-49). Following the general procedure **IV** in Chapter 2, 3-methylcyclopentanone (10 g, 0.10 mol) and 1,1-dimethylhydrazine (23 mL, 0.30 mol) afforded after vacuum distillation (65-75 °C/65-75 mmHg) hydrazone **3-49** (12.5 g, 87%) as an oil. Hydrazone **3-49** (1:1 ratio): ¹H NMR (400 MHz, CDCl₃) δ 0.95-1.01 (m, 3H), 1.16-1.32 (m, 1H), 1.78-1.93 (m, 2H), 1.93-2.09 (m, 1H), 2.18-2.33 (m, 1H), 2.33-2.45 (m, 6H), 2.45-2.68 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 19.7 (CH₃), 19.9 (CH₃), 29.1 (CH₂), 32.2 (CH), 32.4 (CH₂), 32.9 (CH₂), 33.2 (CH₂), 33.2 (CH), 37.9 (CH₂), 41.8 (CH₂), 47.0 (4 CH₃), 175.2 (C), 175.5 (C).

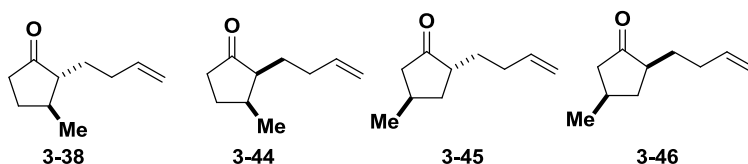


Trimethyl((3-methylcyclopent-1-en-1-yl)oxy)silane (3-41) and **trimethyl((4-methylcyclopent-1-en-1-yl)oxy)silane (3-42).**

Method 1:¹²⁹ A flask with lithium chloride (518 mg, 12.2 mmol) was flame-dried. To this flask was added sequentially anhydrous THF (200 mL) and copper(I) iodide (1.16 g, 6.1 mmol), and a light yellow solution formed. The resulting solution was cooled to -78 °C, followed by the addition of cyclopentenone (10 g, 0.12 mol) and trimethylsilyl chloride (14.6 g, 134 mmol). MeMgCl (3M in THF, 48.8 mL, 147 mmol) was added dropwise over 30 min. The resulting mixture was stirred at -78 °C for another 3 h. The reaction mixture was poured into diethyl ether and saturated aqueous ammonium chloride, and the resulting solution was stirred until a blue transparent solution formed. After the separation, the aqueous layer was extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by vacuum distillation (65-70 °C/15-20 mmHg) to afford a mixture of enol ether **3-41** and **3-42** (9:1 ratio 15.4 g, 74%) as a colorless oil.

Method 2: To a suspension of CuBr·SMe₂ (2.47 g, 12.0 mmol) in diethyl ether (150 mL) at -78 °C under N₂ atmosphere was added MeLi (1.6 M in Et₂O, 15 mL, 24.0 mmol) dropwise via syringe. The resulting suspension was slowly warm to -50 °C, and stirred until most of the solids dissolved. The reaction mixture was cooled to -78 °C again, and HMPA (5.2 mL, 30 mmol) was added slowly. After 20 min, a solution of cyclopentenone (0.99 g, 12 mmol) and trimethylsilyl chloride in Et₂O (18 mL) was added slowly via syringe. After stirring for 4 h at -78 °C, triethylamine (5.0 mL, 36 mmol) was added, and the reaction mixture was stirred at -78 °C for another 2 h. The mixture was poured into saturated aqueous ammonium chloride and pentane. After the separation, the aqueous layer was extracted with pentane three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The concentration afforded enol ether **3-41** (1.4 g, 69%), which was directly used in the next step without further purification.

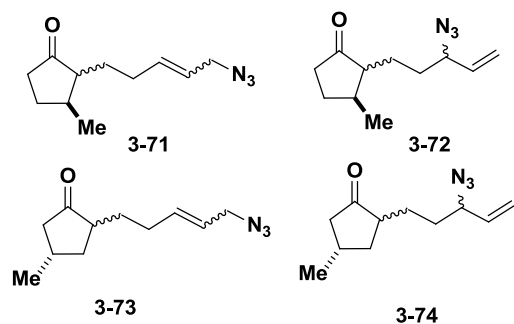
Enol ether **3-41** and **3-42** (9:1 ratio): IR (neat) 2954, 1742, 1643, 1251 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_9\text{H}_{19}\text{OSi}$ ($\text{M}+\text{H}$)⁺ 171.1205, found: 171.1217. Enol ether **3-41**: ^1H NMR (400 MHz, CDCl_3) δ 0.23 (s, 9H), 1.01 (d, $J = 6.8$ Hz, 3H), 1.32-1.41 (m, 1H), 2.03-2.12 (m, 1H), 2.24-2.33 (m, 2H), 2.65-2.76 (m, 1H), 4.60 (q, $J = 1.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ -0.0 (CH_3), 22.4 (CH_3), 30.4 (CH_2), 33.4 (CH_2), 36.4 (CH), 108.9 (CH), 154.2 (C). Enol ether **3-42** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.07 (d, $J = 6.7$ Hz, 3H), 1.83-1.93 (m, 2H), 2.43-2.51 (m, 2H), 4.57 (p, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 0.0 (CH_3), 22.2 (CH_3), 30.1 (CH), 37.2 (CH_2), 41.9 (CH_2), 101.5 (CH), 153.5 (C).



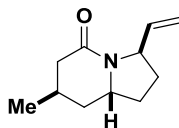
(*2R**,*3S**)-2-(But-3-en-1-yl)-3-methylcyclopentanone (**38**), (*2S**,*3S**)-2-(but-3-en-1-yl)-3-methylcyclopentanone (**3-44**), (*2R**,*4R**)-2-(but-3-en-1-yl)-4-methylcyclopentanone (**3-45**), and (*2S**,*4R**)-2-(but-3-en-1-yl)-4-methylcyclopentanone (**3-46**). Following the general procedure **V** in Chapter 2, hydrazone **3-49** (1:1 ratio, 7.0 g, 50 mmol), freshly-prepared LDA (60 mmol) and 4-bromo-1-butene (8.1 g, 60 mmol) afforded after vacuum distillation (66-70 $^{\circ}\text{C}/5$ mmHg) ketone **3-38**, **3-44**, **3-45**, and **3-46** (42:2:46:10 GC ratio, 6.38 g, 84%) as a colorless oil.

Epimerization: To a solution of ketone **3-38**, **3-44**, **3-45**, and **3-46** (1.52 g, 10 mmol) in methanol (30 mL) was added sodium methoxide (25% w/w in methanol, 2.16 g, 10 mmol) at room temperature. After stirring overnight, saturated aqueous ammonium chloride was

added to quench the reaction. Diethyl ether was used to extract the product, and the aqueous layer was extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (1-2% ethyl acetate/hexanes) to afford ketone **3-38**, **3-44**, **3-45**, and **3-46** (39:5:18:38 GC ratio, 1.20 g, 80%) as a colorless oil. Ketone **3-38**: ^1H NMR (400 MHz, CDCl_3) δ 1.16 (d, $J = 6.2$ Hz, 3H), 1.28-1.44 (m, 1H), 1.55-1.72 (m, 1H), 1.73-1.83 (m, 2H), 1.84-1.96 (m, 1H), 2.02-2.20 (m, 3H), 2.20-2.49 (m, 2H), 4.91-4.98 (m, 1H), 4.99-5.05 (m, 1H), 5.73-5.81 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 220.94 (C), 138.4 (CH), 114.9 (CH_2), 55.7 (CH), 38.0 (CH_2), 37.0 (CH), 31.1 (CH_2), 29.6 (CH_2), 27.0 (CH_2), 19.6 (CH_3). Ketone **3-44** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 0.87 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 220.38 (C), 138.1 (CH), 53.2 (CH), 34.8 (CH_2), 32.7 (CH), 28.0 (CH_2), 23.8 (CH_2), 14.5 (CH_3). Ketone **3-45** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.08 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 221.64 (C), 137.9 (CH), 115.1 (CH_2), 46.5 (CH_2), 46.3 (CH), 36.8 (CH_2), 31.6 (CH_2), 29.7 (CH_2), 28.2 (CH), 20.8 (CH_3). Ketone **3-46** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.14 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 220.72 (C), 138.1 (CH), 115.0 (CH_2), 50.2 (CH), 46.8 (CH_2), 38.5 (CH_2), 28.8 (CH_2), 20.3 (CH_3).

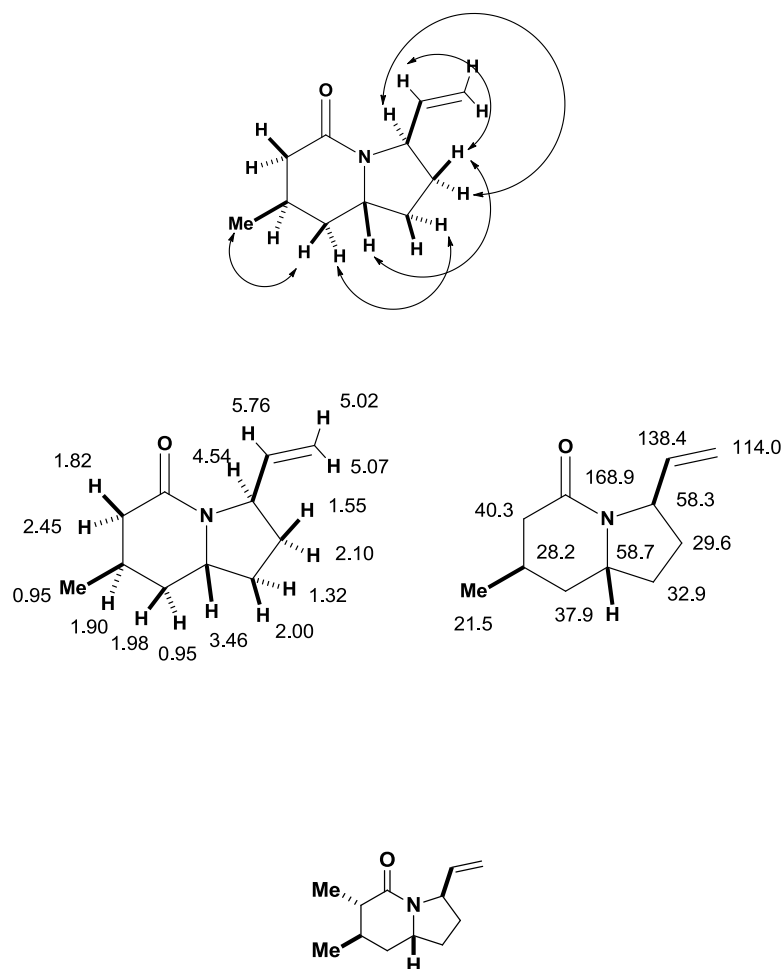


(3*S*^{*})-2-(5-Azidopent-3-en-1-yl)-3-methylcyclopentanone (3-71), (3*S*^{*})-2-(3-azidopent-4-en-1-yl)-3-methylcyclopentanone (3-72), (4*S*^{*})-2-(5-azidopent-3-en-1-yl)-4-methylcyclopentanone (3-73), and (4*S*^{*})-2-(3-azidopent-4-en-1-yl)-4-methylcyclopentanone (3-74). Following the general procedure **III** in Chapter 2, a mixture of ketone **3-38**, **3-44**, **3-45**, and **3-46** (39:5:18:38 GC ratio, 4.18 g, 27.5 mmol) afforded after silica gel column chromatography (1-3% ethyl acetate/hexanes) azides **3-71**, **3-72**, **3-73**, and **3-74** (without determined ratio, 3.64 g, 64%) as a colorless oil. Azides **3-71**, **3-72**, **3-73**, and **3-74**: R_f = 0.45 (10% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 0.87 (d, J = 7.1 Hz, 1H), 1.08 (d, J = 6.4 Hz, 3H), 1.15 (d, J = 6.5 Hz, 9H), 1.30-1.45 (m, 6H), 1.49-1.68 (m, 9H), 1.72 (dd, J = 18.3, 11.5 Hz, 3H), 1.78-1.96 (m, 7H), 2.02-2.20 (m, 21H), 2.20-2.40 (m, 12H), 2.45 (dd, J = 19.0, 7.0 Hz, 2H), 3.69 (d, J = 6.5 Hz, 8H), 3.81 (d, J = 6.7 Hz, 2H), 5.23-5.30 (m, 3H), 5.50-5.58 (m, 5H), 5.67-5.78 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2, 14.5, 19.48, 19.56, 20.25, 20.28, 20.8, 23.7, 24.01, 24.12, 24.8, 25.3, 25.85, 26.06, 27.2, 27.6, 27.9, 28.2, 28.9, 29.52, 29.57, 29.66, 29.82, 30.1, 31.2, 31.6, 32.0, 32.3, 32.8, 34.8, 36.76, 36.81, 37.06, 37.10, 37.91, 37.98, 38.42, 38.47, 38.51, 46.10, 46.41, 46.63, 46.66, 46.72, 50.1, 50.36, 50.42, 52.72, 52.75, 53.1, 55.6, 55.90, 56.01, 60.3, 65.03, 65.12, 65.3, 118.27, 118.31, 118.36, 118.44, 122.81, 122.86, 123.46, 123.59, 123.68, 135.4, 135.5, 135.9, 136.02, 136.11, 136.4, 219.98, 220.20, 220.40, 220.47, 220.8, 221.4.



(3*R,7*R**,8*aR**)-7-Methyl-3-vinylhexahydroindolizin-5(1*H*)-one (3-77).**

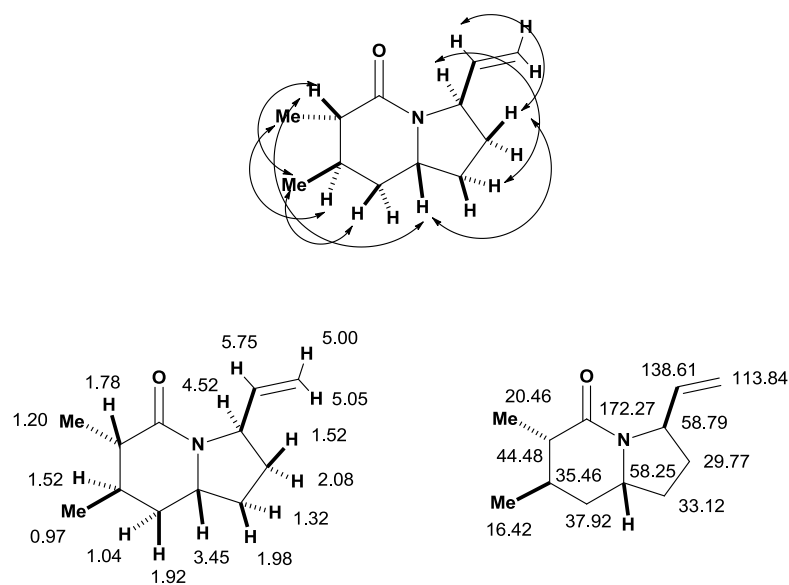
Following the general procedure **VI** in Chapter 2, azides **3-71**, **3-72**, **3-73**, and **3-74** (1.09 g, 5.26 mmol) and titanium tetrachloride (1M in dichloromethane, 8.0 mL, 7.9 mmol) in anhydrous 1,2-dichloroethane (55 mL) afforded after silica gel column chromatography (20-40% ethyl acetate/hexanes) lactam **3-77** (40 mg, 4%) as a colorless oil and a mixture of lactam **3-75** and **3-76** (482 mg + 160 mg, 68%) as a colorless oil. Lactam **3-77**: R_f = 0.60 (EtOAc, twice); ^1H NMR (500 MHz, CDCl_3) δ 0.95 (d, J = 6.3 Hz, 2H), 0.92-1.00 (m, 1H), 1.33 (qd, J = 11.6, 7.9 Hz, 1H), 1.50-1.58 (m, 1H), 1.83 (dd, J = 17.0, 11.6 Hz, 1H), 1.86-1.93 (m, 1H), 1.94-2.03 (m, 2H), 2.10 (dtd, J = 12.9, 8.1, 1.8 Hz, 1H), 2.43-2.49 (m, 1H), 3.46 (tt, J = 10.7, 4.6 Hz, 1H), 4.54 (q, J = 7.7 Hz, 1H), 5.02 (dt, J = 10.3, 1.3 Hz, 1H), 5.07 (dt, J = 17.2, 1.3 Hz, 1H), 5.76 (ddd, J = 17.1, 10.3, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.5 (CH_3), 28.2 (CH), 29.6 (CH_2), 32.9 (CH_2), 37.9 (CH_2), 40.3 (CH_2), 58.3 (CH), 58.7 (CH), 114.0 (CH_2), 138.4 (CH), 168.8 (C). Lactams **3-75** and **3-76** (two portions, diagnostic peaks only): R_f = 0.55 and 0.50 (EtOAc, twice). ^{13}C NMR (125 MHz, CDCl_3) δ 54.1, 55.5, 56.0, 57.7, 58.0, 58.1, 58.3, 58.68, 58.70, 58.9, 60.2, 61.3, 65.0, 113.5, 113.98, 113.99, 114.01, 114.04, 137.7, 137.9, 138.3, 138.4, 168.7, 168.9, 170.2. The following data and NOE correlations were used to assign lactam **3-77**.

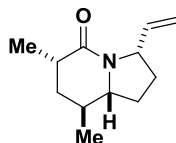


(3*R,6*S**,7*R**,8*aR**)-6,7-Dimethyl-3-vinylhexahydroindolizin-5(1*H*)-one (3-78).**

To a solution of lactam **3-77** (13 mg, 0.07 mmol) in anhydrous THF (10 mL) at -78 °C under N₂ atmosphere was added dropwise freshly-prepared LDA (0.5M in THF, 0.21 mL, 0.11 mmol). After stirring for 1 h, methyl iodide (170 mg, 1.20 mmol) was added dropwise. The reaction mixture is stirred for another 1.5 h, and saturated aqueous ammonium chloride was added to quench the reaction. The mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (15-50% ethyl acetate/hexanes) to afford lactam **3-78** (3.5 mg, 27%) as a colorless oil and lactam **3-79** (0.5

mg, 4%) as a colorless oil. Lactam **3-78**: R_f = 0.40 (100% EtOAc/hexanes); IR (neat) 2927, 1635, 1429, 1322 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{12}\text{H}_{20}\text{NO}$ ($\text{M}+\text{H}$) $^+$ 194.1545, found: 194.1540; ^1H NMR (500 MHz, CDCl_3) δ 0.98 (d, J = 6.5 Hz, 3H), 1.00-1.07 (m, 1H), 1.21 (d, J = 7.2 Hz, 3H), 1.31 (qd, J = 11.8, 7.7 Hz, 1H), 1.47-1.56 (m, 2H), 1.75-1.83 (m, 1H), 1.92 (dt, J = 12.9, 3.4 Hz, 1H), 1.95-2.02 (m, 1H), 2.09 (dtd, J = 12.8, 7.9, 1.7 Hz, 1H), 3.45 (tt, J = 10.7, 4.5 Hz, 1H), 4.53 (q, J = 7.8 Hz, 1H), 5.00 (dt, J = 10.3, 1.3 Hz, 1H), 5.05 (dt, J = 17.2, 1.3 Hz, 1H), 5.75 (ddd, J = 17.1, 10.3, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 16.4 (CH_3), 20.5 (CH_3), 29.8 (CH_2), 33.1 (CH_2), 35.5 (CH), 37.9 (CH_2), 44.5 (CH), 58.3 (CH), 58.8 (CH), 113.8 (CH_2), 138.6 (CH), 172.3 (C). Lactam **3-79** (diagnostic peaks only): R_f = 0.35 (100% EtOAc/hexanes). ^1H NMR (500 MHz, CDCl_3) δ 1.81-1.88 (m, 1H), 1.88-2.02 (m, 3H), 2.05-2.19 (m, 2H), 2.43-2.50 (m, 1H), 3.40-3.51 (m, 1H), 4.54 (q, J = 7.7 Hz, 1H), 4.95-5.11 (m, 2H), 5.76 (ddd, J = 17.1, 10.3, 5.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 37.9, 40.3, 58.3, 58.7, 114.0, 138.4. The following data and NOE correlations were used to assign lactam **3-78**.

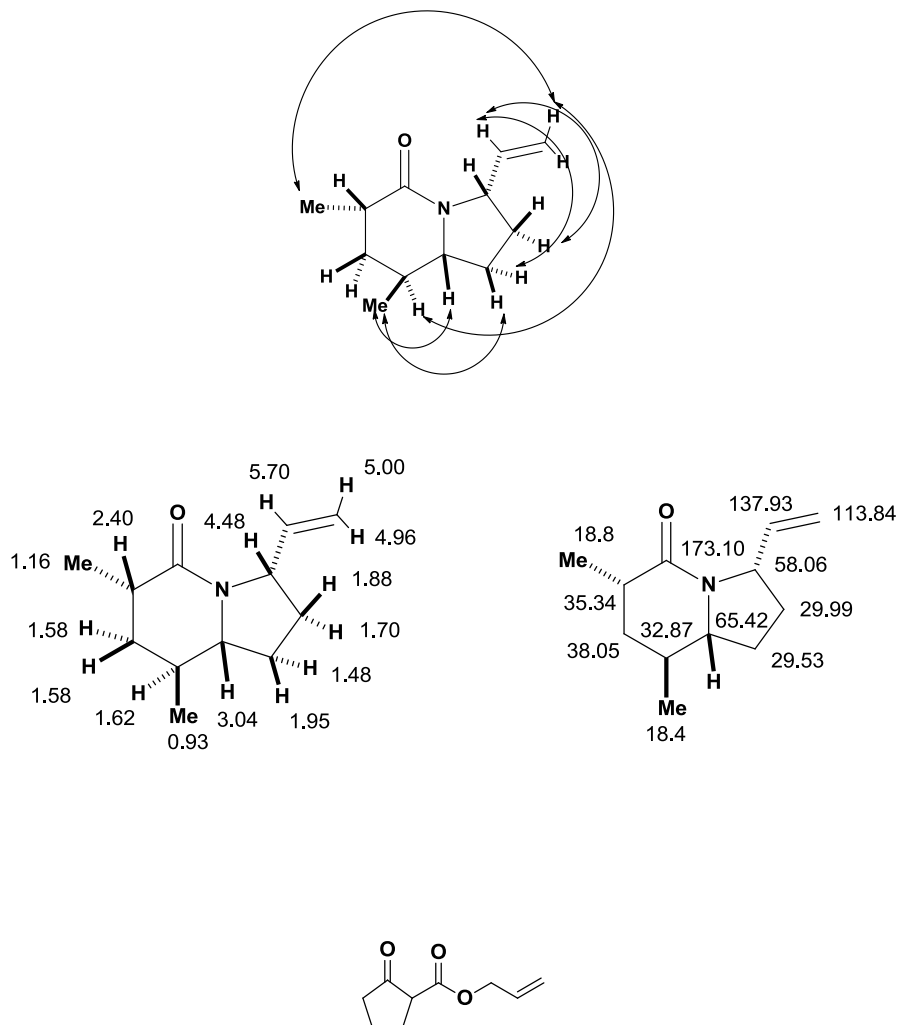




(3*S,6*S**,8*S**,8a*R**)-6,8-Dimethyl-3-vinylhexahydroindolizin-5(1*H*)-one (3-82).**

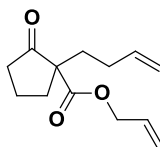
To a solution of a mixture of lactams **3-75** and **3-76** (no ratio, 320 mg, 1.80 mmol) in anhydrous THF (20 mL) at -78 °C under N₂ atmosphere was added dropwise *tert*-butyl lithium (1.7M in pentane, 1.2 mL, 2.0 mmol). The stirring was continued for 1 h, and methyl iodide (0.23 mL, 3.6 mmol) was added dropwise. The stirring was continued for another 2 h, and saturated aqueous sodium bicarbonate was used to quench the reaction. Ethyl acetate was used to extract the product, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (10-40% ethyl acetate/hexanes) to afford lactam **3-82** (20 mg, 6%) as a colorless oil and a mixture of lactams **3-80** and **3-81** (292 mg + 13 mg, 88%) as a colorless oil. Lactam **3-82**: *R*_f = 0.40 (100% EtOAc/hexanes); IR (neat) 2926, 1638, 1422 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₂H₂₀NO (M+H)⁺ 194.1545, found: 194.1548; ¹H NMR (500 MHz, CDCl₃) δ 0.93 (d, *J* = 6.4 Hz, 3H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.42-1.52 (m, 1H), 1.52-1.60 (m, 2H), 1.60-1.66 (m, 1H), 1.69 (dd, *J* = 12.3, 6.1 Hz, 1H), 1.83-1.92 (m, 1H), 1.93-1.99 (m, 1H), 2.36-2.43 (m, 1H), 3.04 (td, *J* = 10.5, 5.0 Hz, 1H), 4.48 (dd, *J* = 7.3, 6.1 Hz, 1H), 4.96 (dt, *J* = 17.1, 1.3 Hz, 1H), 5.00 (dt, *J* = 10.4, 1.2 Hz, 1H), 5.70 (ddd, *J* = 17.1, 10.4, 5.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 18.4 (CH₃), 18.8 (CH₃), 29.5 (CH₂), 30.0 (CH₂), 32.9 (CH), 35.3 (CH), 38.1 (CH₂), 58.1 (CH), 65.4 (CH), 113.8 (CH₂), 137.9 (CH), 173.1 (C). Lactam **3-80** and **3-81**(two portions,

diagnostic peaks only): $R_f = 0.50$ and 0.30 (100% EtOAc/hexanes). ^{13}C NMR (101 MHz, CDCl_3) δ 53.9, 54.9, 58.0, 58.4, 58.9, 64.9, 65.5, 66.5, 113.4, 113.7, 113.8, 114.0, 114.1, 137.8, 137.9, 138.3, 138.7, 172.2, 172.3, 173.0. The following data and NOE correlations were used to assign lactam **3-82**.



Allyl 2-oxocyclopentanecarboxylate (3-91). A solution of ethyl 2-oxocyclopentanecarboxylate (18 mL, 0.12 mol), allyl alcohol (100 mL, 20 mol), and DMAP (1.8 g, 15 mmol) in toluene (100 mL) was refluxed overnight. After cooling to room

temperature, the concentrated residue was directly used for next step without further purification. Ester **3-91**: ^1H NMR (400 MHz, CDCl_3) δ 1.82-1.95 (m, 1H), 2.11-2.22 (m, 1H), 2.25-2.41 (m, 4H), 3.20 (t, $J = 9.1$ Hz, 1H), 4.61-4.71 (m, 2H), 5.26 (dq, $J = 10.4, 1.0$ Hz, 2H), 5.36 (dq, $J = 17.2, 1.5$ Hz, 2H), 5.88-5.98 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.0 (CH_2), 27.4 (CH_2), 38.1 (CH_2), 54.7 (CH), 65.9 (CH_2), 118.5 (CH_2), 131.7 (CH), 169.1 (C), 212.1 (C).



Allyl 1-(but-3-en-1-yl)-2-oxocyclopentanecarboxylate (3-92). A suspension of ketoester **3-91** (~50 mmol), 4-bromo-1-butene (10.12 g, 75 mmol), potassium carbonate (13.8 g, 100 mmol) and sodium iodide (750 mg, 5.00 mmol) in acetone (150 mL) was refluxed overnight. After cooling to room temperature, water and diethyl ether were added to the suspension until it became transparent. After the separation, the aqueous layer was extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography (3-5% ethyl acetate/hexanes) to afford ketoester **3-92** (10.5 g, 92%) as a colorless oil. Ketoester **3-92**: $R_f = 0.65$ (20% EtOAc/hexanes); IR (neat) 2968, 1751, 1725, 1154 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 245.1154, found: 245.1156; ^1H NMR (400 MHz, CDCl_3) δ 1.61-1.72 (m, 1H), 1.88-2.13 (m, 6H), 2.22-2.32 (m, 1H), 2.37-2.47 (m, 1H), 2.51-2.60 (m, 1H), 4.60 (dt, $J = 5.6, 1.3$ Hz, 2H), 4.95 (d, $J = 10.0$ Hz, 1H), 5.02 (dq, $J = 17.2, 1.4$ Hz, 1H), 5.23 (dq, $J = 10.4, 1.2$ Hz, 1H), 5.31 (dq, $J = 17.2, 1.4$ Hz, 1H), 5.71-5.82 (m, 1H), 5.83-5.93 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.6 (CH_2),

29.1 (CH₂), 32.8 (CH₂), 33.0 (CH₂), 37.9 (CH₂), 60.2 (C), 65.8 (CH₂), 115.1 (CH₂), 118.5 (CH₂), 131.6 (CH), 137.6 (CH), 170.5 (C), 214.4 (C).

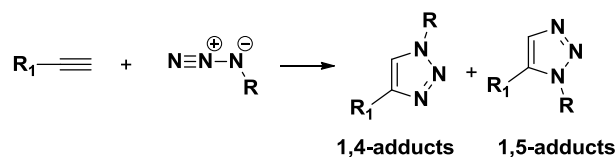
CHAPTER 4

THE APPLICATION OF HYDROXYL ALLYLIC AZIDE

4.1 Introduction

Having experienced combination of allylic azide rearrangement and intramolecular Schmidt reaction, we considered on the development of the combination between isomeric allylic azides and other reactions. This chapter describes initial studies of the combination between allylic azide rearrangement and intramolecular azide-alkyne Huisgen cycloaddition reaction.

Azide-alkyne cycloaddition (AAC) can couple an azide and a terminal or internal alkyne to form a 1,2,3-triazole via a formal 1,3-dipolar cycloaddition, which can occur intermolecularly or intramolecularly (Scheme 88). This reaction has been extensively reviewed.¹³⁷⁻¹⁴⁰ Copper-catalyzed AAC reaction (CuACC) has been known as "the cream of the crop" of click chemistry, a term coined by Sharpless and coworkers.¹⁴¹ A click reaction is defined as a reaction with the properties of wide scope, high atom economy, rate and very high exothermicity.



Scheme 88. Azide-alkyne cycloaddition.

For intermolecular AAC reaction,¹³⁹ there is two possible thermal triazoles, 1,4- and 1,5-regioisomers with ca. 1:1 ratio, whose activation barriers (~26 kcal/mol) are pretty similar

for concerted mechanism by computational studies.¹⁴² However, both reactions are highly exothermic, releasing ~61 kcal/mol en route to either isomer. The discovery of new metal catalysts has conferred new life for this reaction. Copper is the most common catalyst in this reaction and it selectively results in the formation of the 1,4-regioisomer. Ruthenium catalyst can produce the alternative 1,5-isomer as the major product. Tetraalkylammonium hydroxide has also been reported to catalyze this reaction affording 1,5-adducts with high yield and high regioselectivity.¹⁴³

Sharpless and coworkers reported the mechanistic DFT studies on the CuAAC reaction (Figure 118).¹⁴² The rate-determining step is the conversion of alkyne and azide coordinate copper species **4-6** to an unusual six-membered copper(III) metalacycle intermediate **4-7** with 15 kcal/mol activation barrier. In comparison with purely thermal condition, a 10^7 - 10^8 rate acceleration was expected from computational studies, which matched observed experimental results. Based on the mechanistic studies, only terminal alkynes are preferred substrates for CuAAC reaction. Furthermore, several side reactions are also involved in this reaction. Copper acetylide **4-3** can polymerize to **4-4**, the hydrolysis of which upon work-up affords the starting alkyne. Intermediate **4-8** can be easily oxidized or coupled to give by-products **4-10**, **4-11**, or **4-12**.

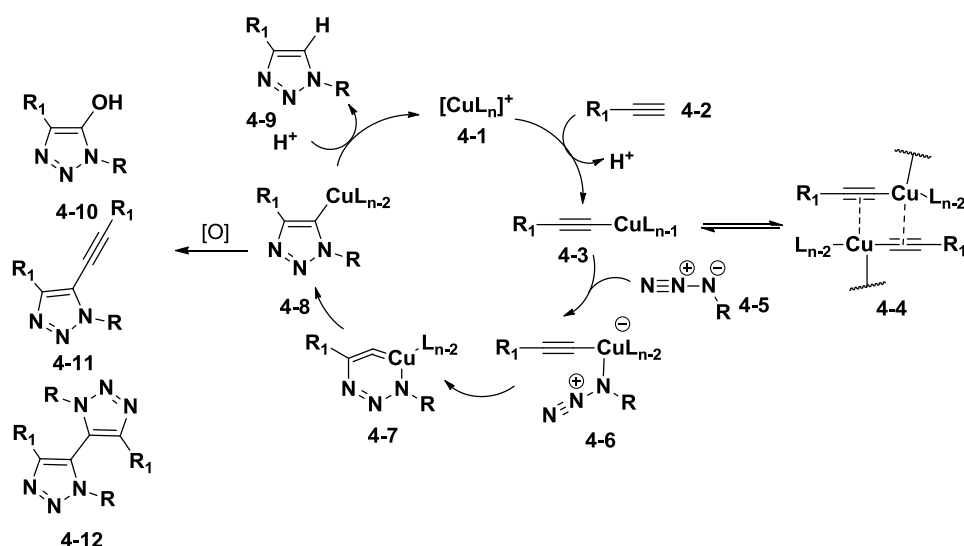


Figure 118. The mechanism of CuAAC reaction.

Copper(I) reagents, which are the least thermodynamically stable among three oxidation states of copper (0, +1 and +2), have been most commonly utilized in this CuAAC reaction.^{137,138} In addition, copper (II) catalysts can be easily reduced *in situ* to copper(I) catalyst by amines, alcohols, acids, and promote the catalytic cycle. Studies showed by Fokin that the combination of copper sulfate and sodium ascorbate is a very convenient and practical procedure for CuAAC reaction.

Cu(I) iodide should be avoided due to iodide anion's ability to act as a bridge ligand for the metal, and this can result in the formation of poly copper acetylides to terminate the catalytic cycle. This polymerization can be inhibited by the addition of amine ligands (not additives or bases) (Figure 119). Those amine ligands can also a) increase the solubility of copper(I) catalyst, b) facilitate the coordination of azide and alkyne to metal, and c) protect the copper(I) from the oxidation. All the influences of amine ligands can contribute to enhance the reaction rate.

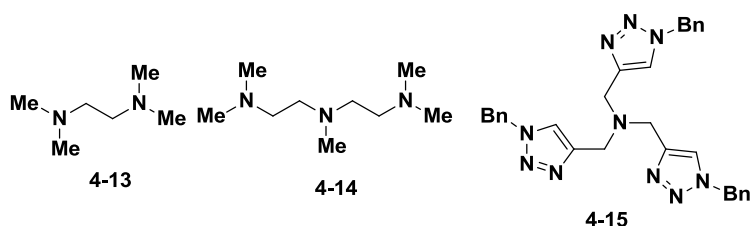
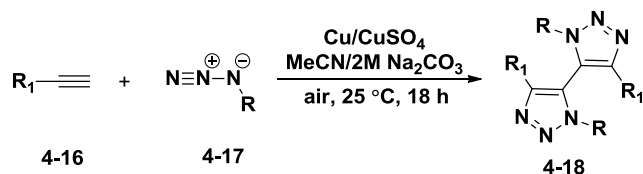


Figure 119. Amine ligands.

Burgess and coworkers reported the synthesis of bistriazoles using Cu(I) catalyst (Scheme 89).¹⁴⁴ They found that this reaction was dependent on the base used, with the best results obtained in aqueous sodium carbonate.



Scheme 89. Synthesis of bistriazoles.

Fokin and coworkers reported the ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) to generate 1,5-adducts with very high regio-selectivity (Figure 120).¹⁴⁵ DFT computational studies were used to explain their experimental results. In this catalytic cycle, the rate-determining step is the conversion of alkyne and azide coordinate ruthenium species **4-22** to the unusual six-membered ruthenacycle intermediate **4-23** with a 4.3 kcal/mol activation barrier. Based on this mechanistic study, both terminal and internal alkynes can be the substrates for this conversion.

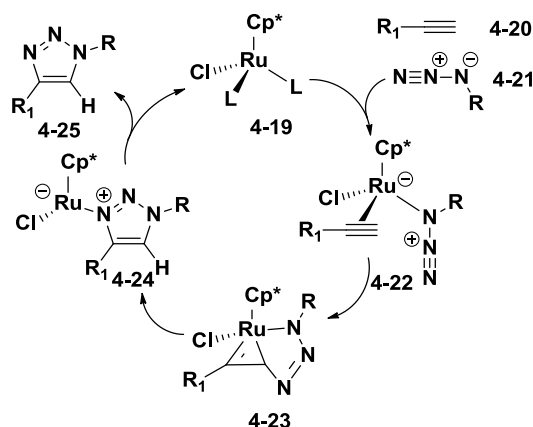
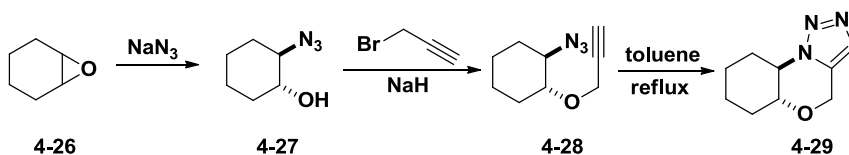


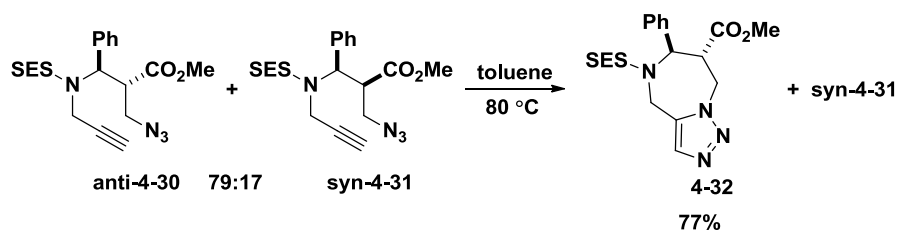
Figure 120. The mechanism of RuAAC reaction.

Most intramolecular AAC reactions are thermally conducted to produce fused bicyclic triazoles. For example, Datta and coworkers have reported a feasible sequence to prepare [5,6]-fused bicyclic triazoles (Scheme 90).¹⁴⁶ The cycloaddition precursor **4-28** was easily prepared by epoxide opening and subsequent alkylation from cyclohexene epoxide.



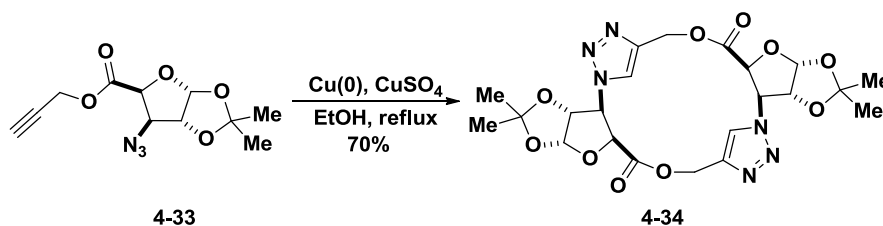
Scheme 90. Datta's sequence to prepare [5,6]-fused bicyclic triazoles.

Declerck and coworkers reported the synthesis of [7,5]-fused triazoles, in which only the anti isomer is the suitable starting material with unreacted syn isomer due to its steric inference between two neighboring groups (Scheme 91).¹⁴⁷ This reaction suggested that it might be possible to achieve good selectivity in the combination of allylic azide rearrangement and AAC reaction.



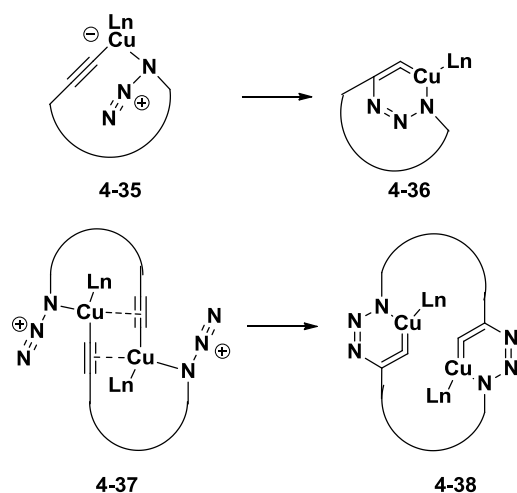
Scheme 91. Selectivity in the intramolecular AAC reaction.

Chandrasekhar and coworkers observed the dimerization and trimerization of ACC reaction in high yield utilizing an in-situ generated Cu(I) catalyst (Scheme 92).¹⁴⁸ Due to the inherent 1,4-regioisomer formation utilizing copper(I) catalyst, the dimer has high possibility to be formed in comparison with highly strained monomer.



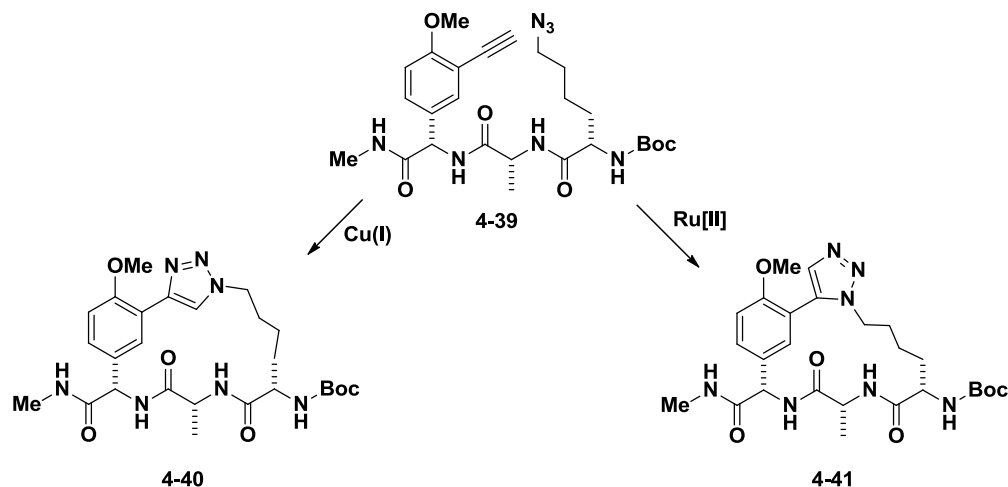
Scheme 92. Dimerization of ACC reaction.

Burgess and coworkers utilized the exo-like dimerized copper acetylide **4-37** to explain why dimerization is the major pathway in this CuAAC reaction (Scheme 93).¹⁴⁹ Copper catalyst can coordinate two alkyne species to make the intermediate stable in the catalytic cycle. Azide of the second molecule reacted with the triple bond of the first molecule to form a more stable intermediate, and then facilitated the dimerization in this reaction.



Scheme 93. Explanation of dimerization in the CuAAC reaction.

Liskamp and coworkers reported the syntheses of the diverse macrocycles with 1,4- and 1,5-regioisomers, utilizing CuAAC and RuAAC reaction respectively (Scheme 94).¹⁵⁰

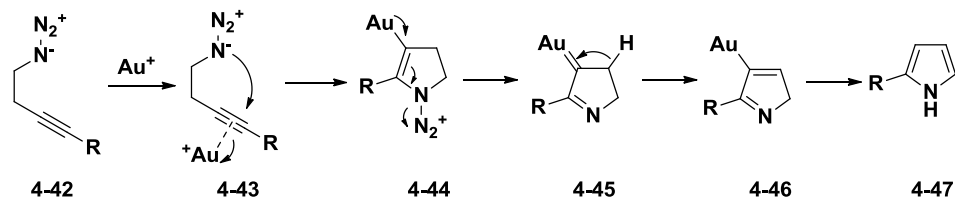


Scheme 94. Intramolecular CuAAC and RuAAC reaction.

Besides azide-alkyne cycloaddition to prepare triazoles, we are also interested in other transformations starting from the similar starting materials.

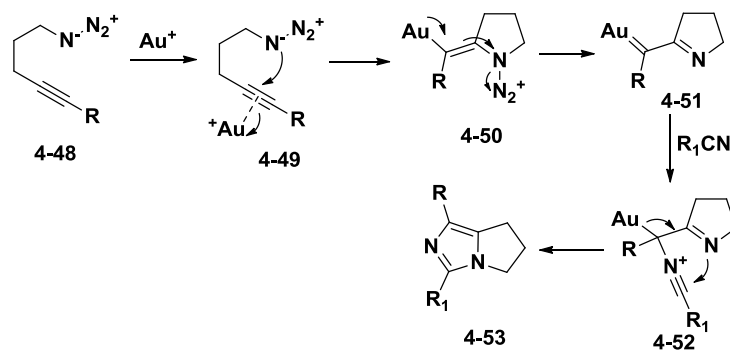
In 2005, Toste and coworkers reported gold-catalyzed pyrrole synthesis starting from azide-alkyne to give 5-endo-dig cyclization product **4-44** (Scheme 95).¹⁵¹ The extrusion of

nitrogen gas afforded **4-45**, and hydrogen migration and tautomerization afforded the pyrrole **4-47**.



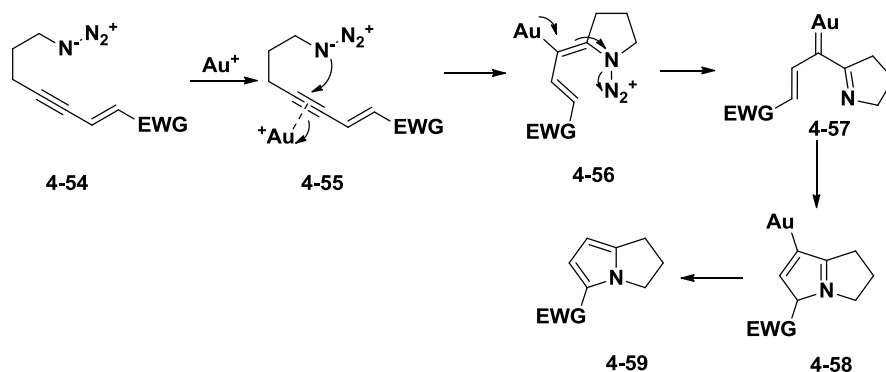
Scheme 95. Gold-catalyzed pyrrole synthesis.

Zhang and coworkers reported the synthesis of bicyclic imidazoles using a related [2+3] cycloaddition (Scheme 96).¹⁵² In this transformation, 5-exo-dig cyclization was utilized to generate α -imino gold carbene intermediate, and the following attack of nitrile and cyclization afforded product **4-53**.



Scheme 96. Gold-catalyzed azide-alkyne-nitrile reaction.

They also reported the synthesis of 2,3-dihydro-1*H*-pyrrolizines utilizing the similar strategy (Scheme 97).¹⁵³ After the 5-exo-dig cyclization, Nazarov electrocyclozation and tautomerization afforded the pyrrolizine derivative **4-59**.



Scheme 97. Gold-catalyzed pyrrolizine synthesis.

4.2 Allylic azide rearrangement-involved combinations.

Based on the stereo-control results in the combination of allylic azide rearrangement and intermolecular Schmidt reaction, we speculated that high selectivity could be obtained for the combination of allylic azide rearrangement and thermal intramolecular azide-alkyne cycloaddition (Figure 121). [5,6]-Fused bicyclic triazoles **4-64** and **4-66** should be the major products due to the slow formation of 8-membered ring to generate **4-65**. Stereoselectivity could be controlled by the substituents in the substrates.

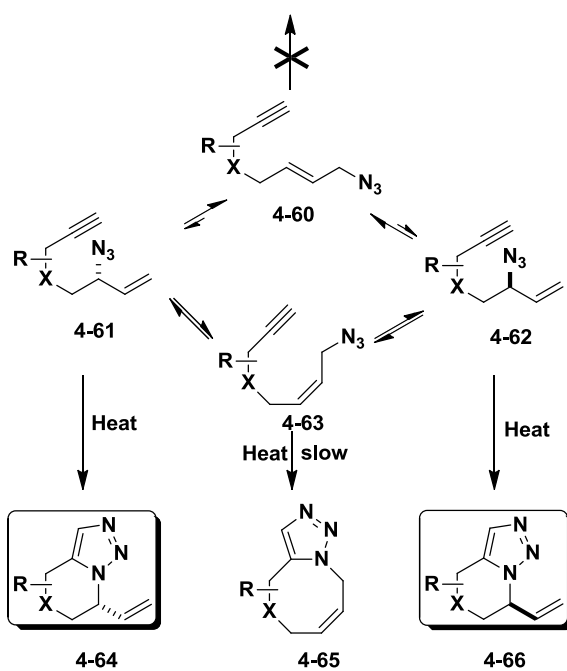


Figure 121. Allylic azide-involved thermal AAC reaction.

Based on the mechanism of RuAAC reaction, productive intermediate **4-68** can only be generated from **4-63**, and not from **4-61** or **4-62** due to the ring strain (Figure 122). Triazole **4-65** should be the sole product in this reaction.

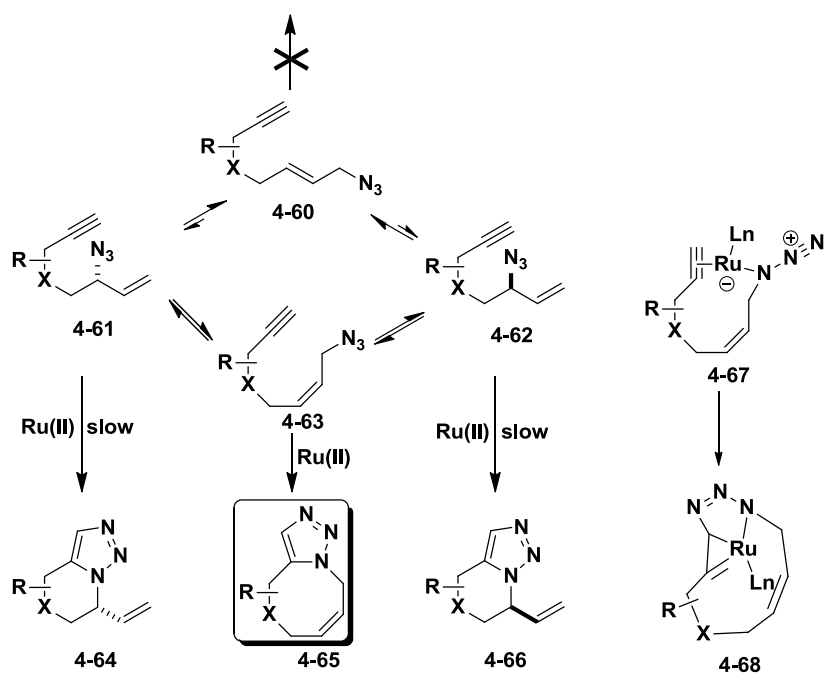


Figure 122. Combined allylic azide and thermal RuAAC reaction.

Based on the mechanism of CuAAC reaction, unusual six-membered copper intermediate **4-70** can only be generated from **4-63**, and not from **4-61** or **4-62** due to the ring strain (Figure 123). Triazole **4-71** should be the major product in this reaction. If the intermediate ring is not big enough, dimerization to **4-72** may occur instead (see above).

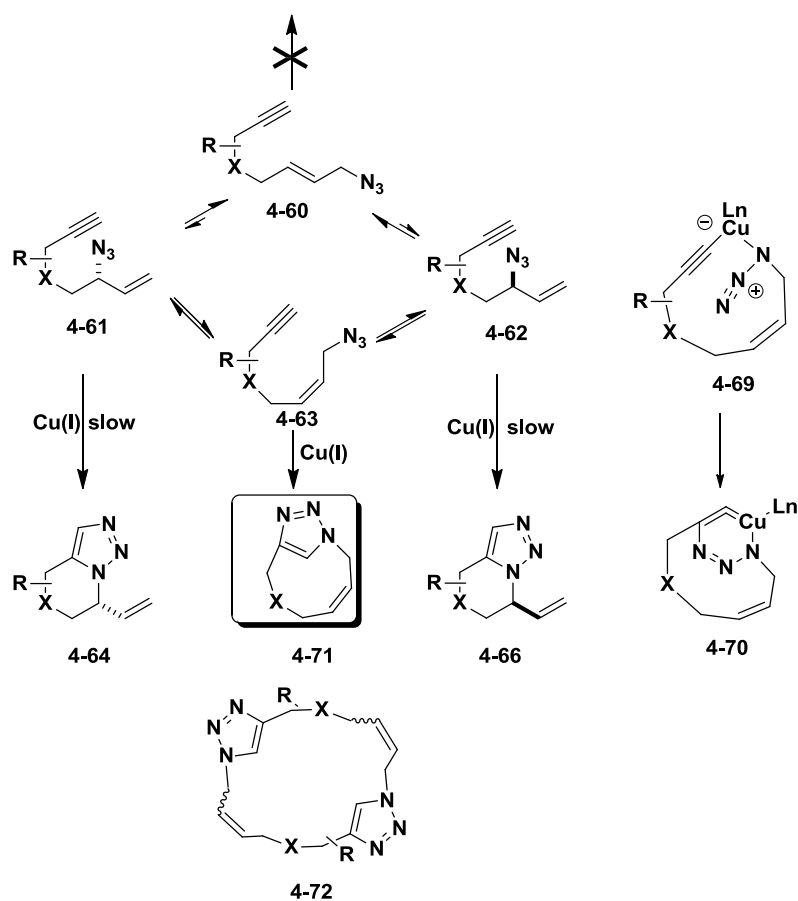


Figure 123. Allylic azide-involved CuAAC reaction.

Allylic azide alkynes could be employed for gold-catalyzed pyrrole synthesis to afford vinyl-substituted pyrrole **4-79** (Figure 124).

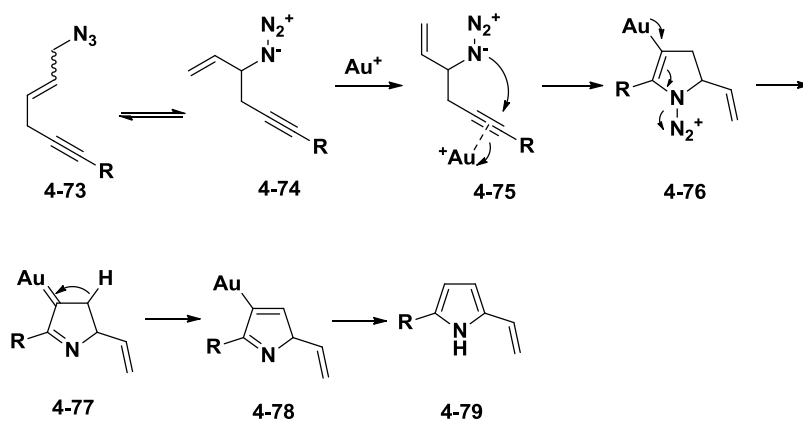


Figure 124. Gold-catalyzed allylic azide-involved pyrrole synthesis.

Allylic azide alkynes are to be tested for gold-catalyzed imidazole synthesis to afford vinyl-substituted bicyclic imidazole **4-86** (Figure 125).

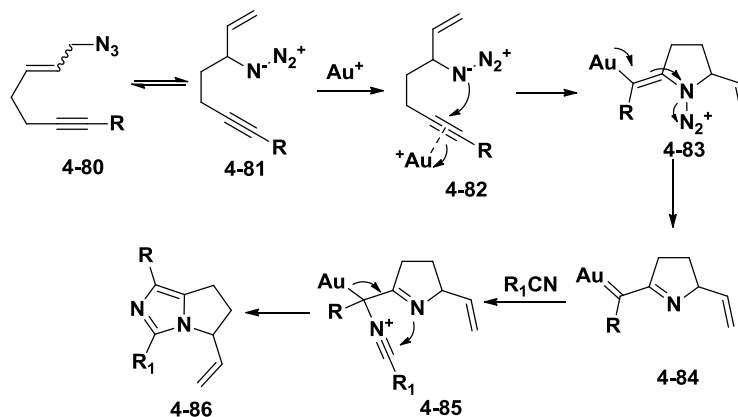


Figure 125. Gold-catalyzed synthesis of bicyclic imidazoles.

Diversity-oriented synthesis (DOS) is a strategy to quickly access a diverse pool of molecules from common intermediate utilizing different types of organic reactions. In principle, allylic azide may serve as precursors to a variety of diversified scaffolds using the reactions described above (Figure 126).

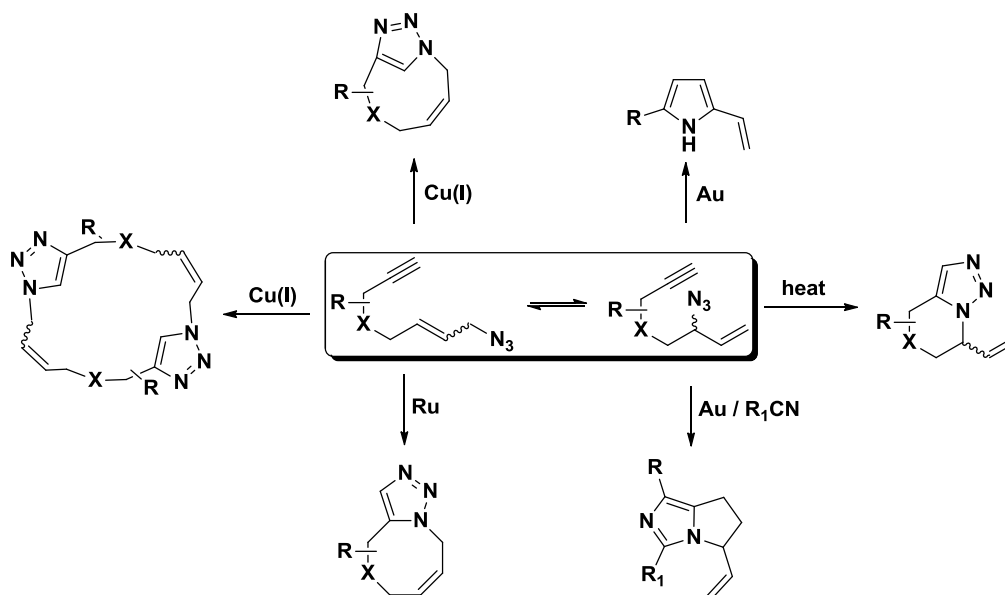
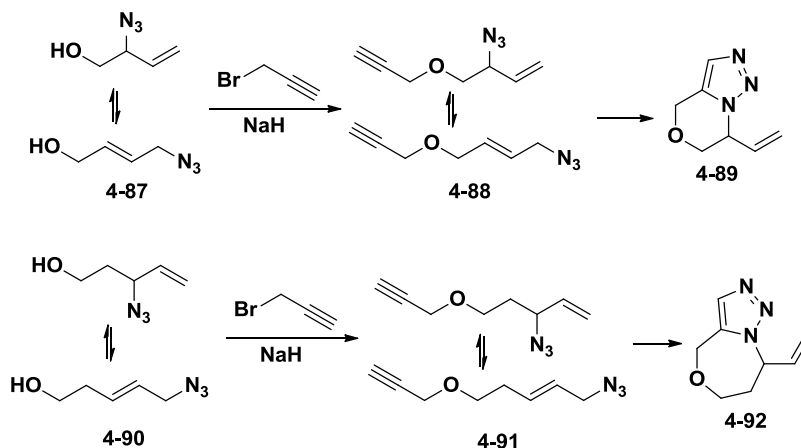


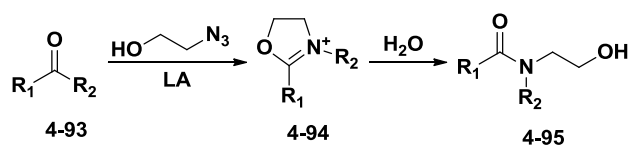
Figure 126. Summarized allylic azide-involved combination with other reactions.

Hydroxyl allylic azide is a good partner for the synthesis of allylic azide alkynes **4-88** and **4-91** (Scheme 98).



Scheme 98. Preparation of allylic azide alkynes.

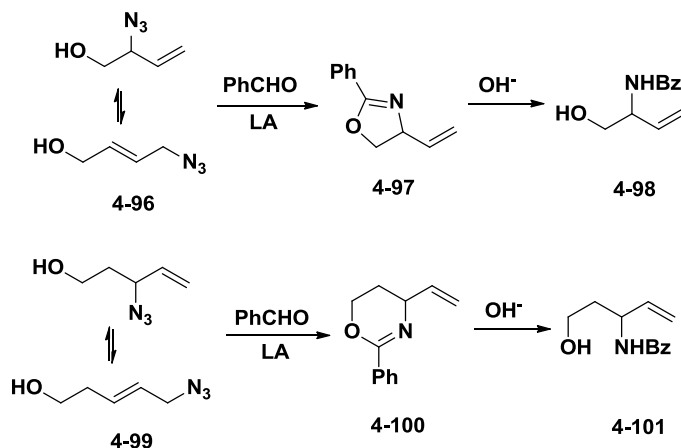
Other than Schmidt reaction, our group has also developed hydroxyl azide involved-Boyer reaction (Scheme 99).¹⁵⁴ Under the promotions of Lewis acid, hydroxyl azide can react with ketone or aldehyde **4-93** to dihydrooxazolium ion **4-94**, followed by the hydrolysis to **4-95**.



Scheme 99. Boyer reaction.

Based on the successful experience of the combination of allylic azide rearrangement and intramolecular Schmidt reaction, we can speculate that hydroxyl allylic azides **4-96** and **4-99** can be combined with Boyer reaction to give **4-98** and **4-101**, respectively (Scheme 100). From the perspective of nitrogen's oxidation state, **4-98** and **4-101** are the reduced forms of azides **4-96** and **4-99**, and benzaldehyde was oxidized to benzoyl group, the protective group

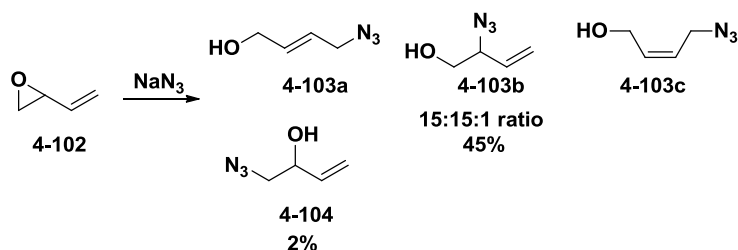
of amine. Hence, this reaction is also a selective reduction of a mixture of terminal and internal allylic azides, which can not be achieved by conventional methods.



Scheme 100. Boyer reaction mediated allylic azide reduction.

4.3 Combination of allylic azide rearrangement with azide-alkyne cycloaddition.

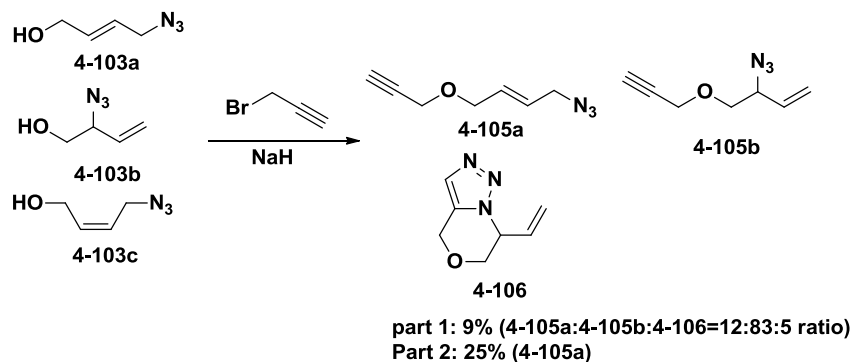
A mixture of hydroxyl allylic azides **4-103a**, **4-103b** and **4-103c** was prepared from 2-vinyloxirane with sodium azide in a 45% yield, along with 2% other regioisomer **4-104** (Scheme 101).



Scheme 101. Preparation of hydroxyl allylic azides **4-103**.

The alkylation of **4-103** was accomplished using sodium hydride with propargyl bromide to afford a mixture of allylic azide **4-105a**, **4-105b** and triazole **4-106** with 83:12:5 ratio in 9% yield, and pure **4-105a** with 25% yield after silica gel column chromatography

(Scheme 102). This result showed that the interconversion between **4-105a** and **4-105b** was not fast, and then a single pure isomer could be isolated.



Scheme 102. Alkylation of allylic azides **4-103**.

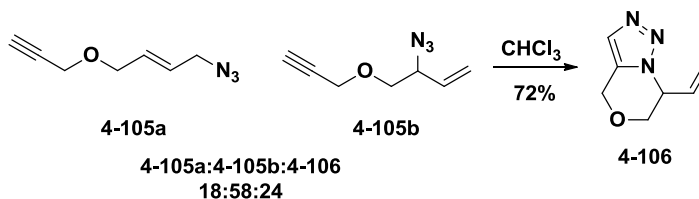
We speculated that cycloaddition may happen during the separation or concentration steps. In any way, this cycloaddition is exothermic with very low activation barrier, and it can happen naturally. Then we used ^1H NMR to track its ratio change with time (Table 41). The conversion for both isomers to triazole **4-106** is above 85% after 45 days. The initial rate for azide **4-105a** to triazole **4-106** is much slower than that of azide **4-105b**'s.

Table 41. Ratio change in the cycloaddition.

Time	Ratio (4-105b: 4-105a: 4-106)	Ratio (4-105b: 4-105a: 4-106)
0 d	83:12:5	0:100:0
1 d	36:45:18	18:80:3
2 d	25:52:23	20:75:6
2.5 d	21:52:26	21:71:8

3.5 d	18:52:30	21:67:13
6.5 d	15:45:39	17:59:24
18 d	10:27:64	11:34:55
38 d	4:11:85	5:16:79
45 d	4:7:89	3:12:85

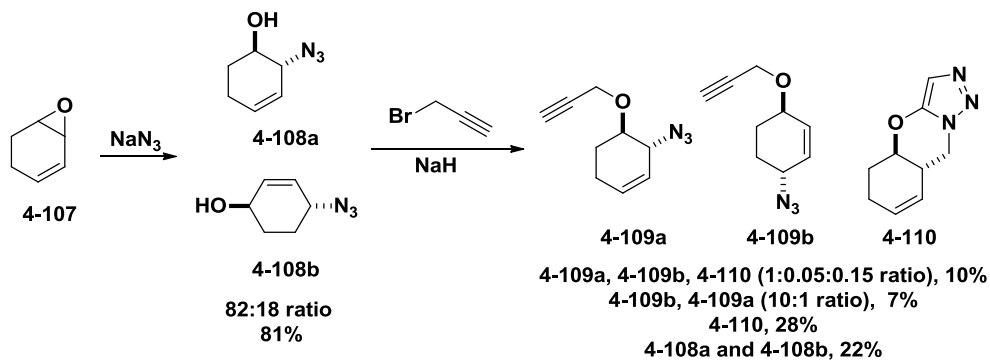
A mixture of allylic azides **4-105a**, **4-105b** and triazole **4-106** with 18:58:24 ratio was refluxed in chloroform for 4 h to afford triazole **4-106** in 72% yield (Scheme 103).



Scheme 103. Cycloaddition to triazole **4-106**.

Allylic azides **4-108a** and **4-108b** were prepared through the opening of epoxide **4-107** by sodium azide in 81% yield with 82:18 ratio (Scheme 104). Why azide **4-108a** is more thermodynamic than **4-108b** is because of hydrogen bonding between hydroxyl group and azide. The alkylation afforded multiple products with 28% unreacted starting allylic azides. Alkylated products **4-109a** and **4-109b** were isolated as the major isomers in 10% and 7% yields respectively. Cyclized triazole **4-110** was also obtained in 28% yield, whose structure was confirmed by X-ray crystallography (Figure 127). We also noticed that the initial ratio of **4-109a**, **4-109b** and **4-110** was changed from 1:0.1:0.15 to 0.1:0.1: 1 ratio after 7 days; after 14 days, the ratio was 1:1:40. For the portion with **4-109b** as the major product, the initial

ratio of **4-109a**, **4-109b** and **4-110** was changed from 1:10:0 to 0.4:0.3:1 ratio after 7 days; after 14 days, the ratio is 1:1:20.



Scheme 104. The synthesis of triazole **4-110**.

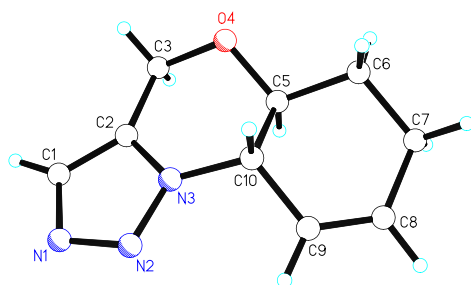
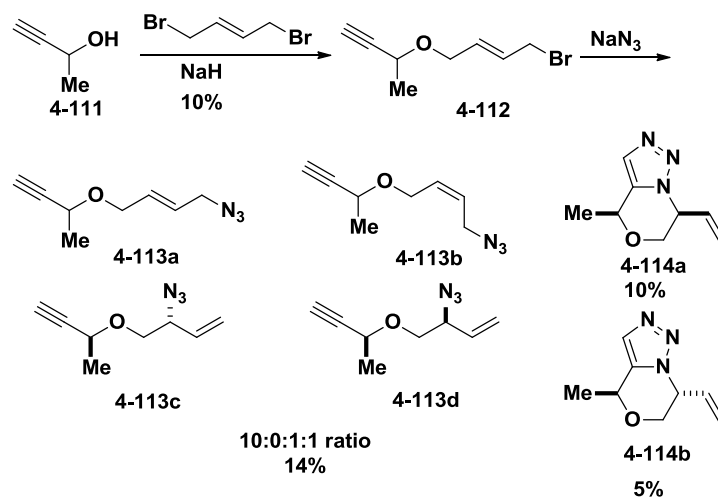


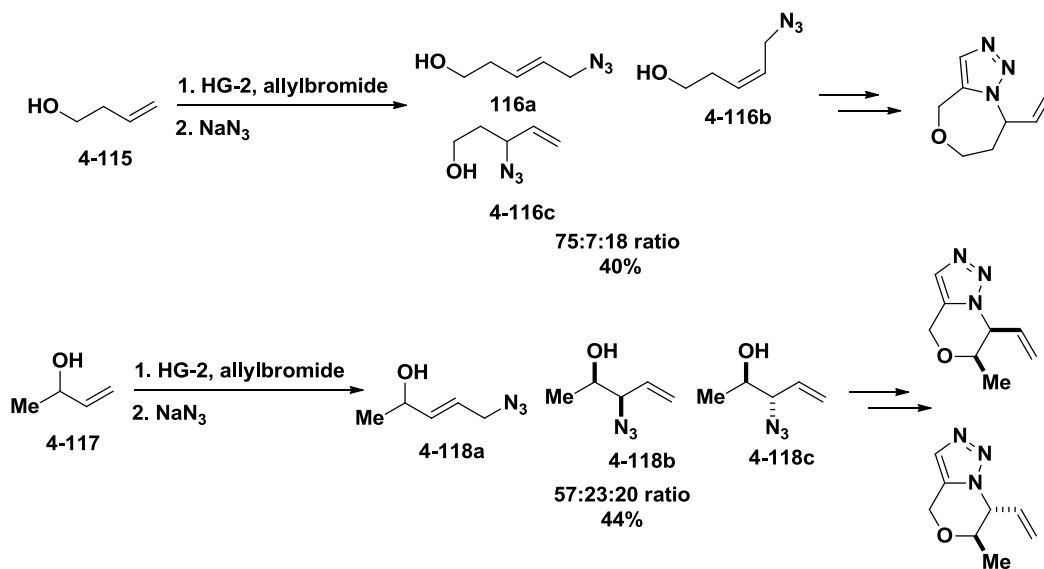
Figure 127. ORTEP representation of triazole **4-110**.

The alkylation of propargyl alcohol **4-111** with 1,4-dibromobut-2-ene gave low yield, and its further optimization is in progress (Scheme 105). The following azide displacement also afforded triazoles **4-114a** and **4-114b** with 10% and 5% yield respectively, along with a mixture of allylic azides **4-113a**, **4-113b**, **4-113c** and **4-113d** (10:0:1:1) in 14% yield. The structures of **4-114a** and **4-114b** were confirmed by 2D NMRs.



Scheme 105. The synthesis of triazole **4-114a** and **4-114b**.

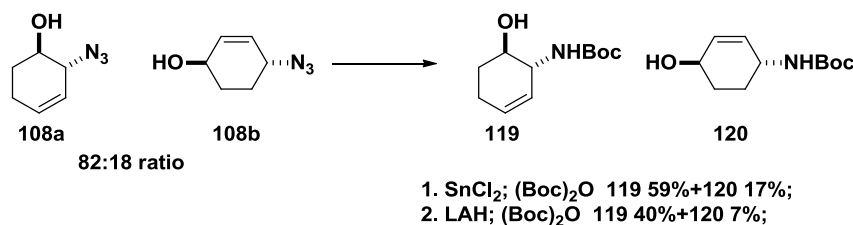
In order to expand the scope of this combination, allylic azides **4-116** and **4-118** were prepared in a 5-gram scale, following the general procedure in Chapter 2 (Scheme 106)..



Scheme 106. The preparation of allylic azides **4-116** and **4-118**.

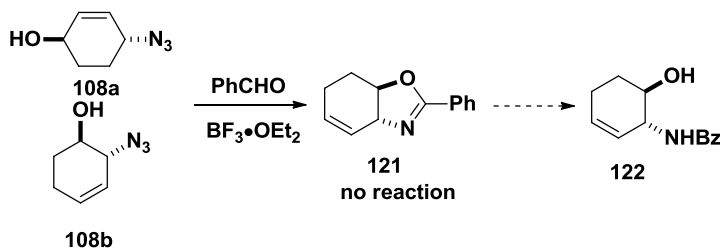
4.4 Reduction of hydroxyl allylic azides.

We first conducted the reduction of allylic azides under conventional conditions, to find out the difference of selectivity for the normal reduction and the combination of Boyer reaction and hydrolysis, the latter being considered to be highly selective. The azides **4-108a** and **4-108b** were reduced under the assistance of tin(II) chloride and the following Boc protection afforded carbamate **4-119** and **4-120** with 4:1 ratio, which has the similar ratio as starting materials (Scheme 107). Higher selectivity (6:1 ratio) was obtained from LAH reduction and Boc protection.



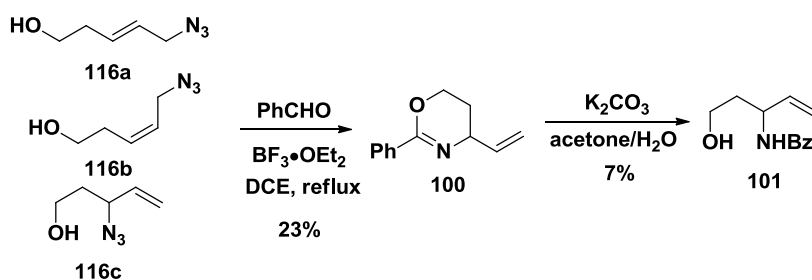
Scheme 107. Reduction of allylic azides **4-108**.

In order to make comparison, the Boyer reaction and hydrolysis sequence to **4-122** were studied. However, the Boyer reaction didn't work for this substrate. This might be resulted from ring strain of trans [5,6]-fused bicyclic **4-121** (Scheme 108).



Scheme 108. Boyer reaction and hydrolysis to **4-122**.

The similar combination to **4-101** was tested for allylic azides **4-116**, which can not produce strained dihydrooxazole (Scheme 109). Low yields are obtained for both reactions, and their optimizations are in progress.

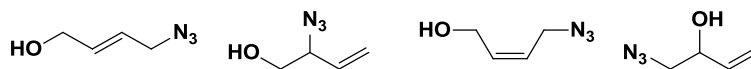


Scheme 109. Boyer reaction and hydrolysis to **4-101**.

4.5 Conclusion

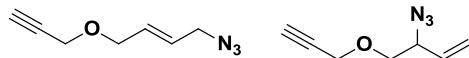
Initial studies were conducted for the combination of allylic azide rearrangement and azide-alkyne cycloaddition. This reaction could occur at room temperature with low activation energy barrier. Four vinyl-substituted bicyclic triazoles were synthesized, one of which was confirmed by X-ray crystallography. The selective reduction of allylic azides was also studied. The comparison between normal reduction and the combination for allylic azide-Boyer reaction and hydrolysis was conducted. The further optimization of these reactions is planned.

4.6 Experimental data



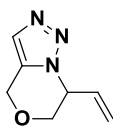
(E)-4-Azidobut-2-en-1-ol (103a), **2-azidobut-3-en-1-ol (4-103b)**, **(Z)-4-azidobut-2-en-1-ol (4-103c)**, and **1-azidobut-3-en-2-ol (4-104)**. To a solution of 2-vinylloxirane (370 mg, 5.28 mmol) and ammonium chloride (1.41 g, 26.4 mmol) in a mixed solvent of ethanol (16 mL) and water (2 mL), was added sodium azide (3.43 g, 52.8 mmol). The resulting mixture was refluxed for 24 h. After it was cooling to room temperature, water and dichloromethane were added. After separation, the aqueous layer was extracted with dichloromethane three

times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (10-20% EtOAc/hexanes) to afford **4-104** (10 mg, 2%) as a colorless oil and a mixture of azides **4-103a**, **4-103b**, and **4-103c** (15:15:1 ratio, 270 mg, 45%) as a colorless oil. Azide **4-103a**, **4-103b**, and **4-103c**: R_f = 0.30 (50% EtOAc/hexanes). Azide **4-103a**: ^1H NMR (400 MHz, CDCl_3) δ 2.28 (br, 1H), 3.79 (d, J = 6.4 Hz, 2H), 4.19 (d, J = 6.4 Hz, 2H), 5.73-5.80 (m, 1H), 5.88-5.96 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 52.2 (CH_2), 62.5 (CH_2), 124.1 (CH), 134.4 (CH). Azide **4-103b**: ^1H NMR (400 MHz, CDCl_3) δ 2.54 (br, 1H), 3.53-3.57 (m, 1H), 3.63-3.67 (m, 1H), 4.03-4.07 (m, 1H), 5.36-5.43 (m, 2H), 5.73-5.80 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 64.6 (CH_2), 66.4 (CH), 120.2 (CH_2), 132.0 (CH). Azide **4-103c** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 2.12 (br, 1H), 3.87 (d, J = 6.8 Hz, 2H), 4.23 (d, J = 6.8 Hz, 2H). Azide **4-104**: R_f = 0.45 (50% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 2.08 (br, 1H), 3.33 (dd, J = 7.2 Hz, 12.3 Hz, 1H), 3.40 (dd, J = 3.6 Hz, 12.3 Hz, 1H), 4.34 (br, 1H), 5.28 (dt, J = 10.4 Hz, 1.2 Hz, 1H), 5.41 (dt, J = 17.2 Hz, 1.2 Hz, 1H), 5.85-5.93 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 56.4 (CH_2), 72.0 (CH), 117.2 (CH_2), 136.9 (CH).



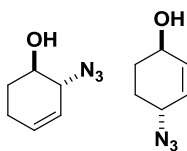
(E)-1-Azido-4-(prop-2-yn-1-yloxy)but-2-ene (4-105a) and **3-Azido-4-(prop-2-yn-1-yloxy)but-1-ene (4-105b)**. To a solution of a mixture of azides **4-103a**, **4-103b**, and **4-103c** (500 mg, 4.42 mmol) in anhydrous DMF (20 mL) at 0 °C under N₂ atmosphere was added sodium hydride (60% in mineral oil, 221 mg, 5.52 mmol). After the resulting mixture was stirred at 0 °C for 30 min, propargyl bromide (80% w/w in toluene, 821 mg, 5.52 mmol) was added slowly. The resulting mixture was stirred overnight, and quenched with saturated aqueous ammonium chloride. Products were extracted with diethyl ether three times. The

combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0.5-2% EtOAc/hexanes) to afford a mixture of azides **4-105a**, **4-105b**, and triazole **4-106** (12:83:5 ratio, 60 mg, 9%) as a colorless oil and azide **4-105a** (165 mg, 25%) as a colorless oil. Azide **4-105a**: R_f = 0.30 (5% EtOAc/hexanes); IR (neat) 2859, 2100 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_7\text{H}_{10}\text{N}_3\text{O}$ ($\text{M}+\text{H}$)⁺ 152.0824, found: 152.0830; ^1H NMR (400 MHz, CDCl_3) δ 2.46 (t, J = 2.4 Hz, 1H), 3.80 (d, J = 4.6 Hz, 2H), 4.11 (d, J = 4.1 Hz, 2H), 4.17 (d, J = 2.4 Hz, 2H), 5.84 (q, J = 4.8 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 52.2 (CH_2), 57.3 (CH_2), 69.0 (CH_2), 74.7 (CH), 79.4 (C), 126.6 (CH), 130.7 (CH). Azide **4-105b**: R_f = 0.40 (5% EtOAc/hexanes); IR (neat) 2859, 2100, 1089 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_7\text{H}_{10}\text{N}_3\text{O}$ ($\text{M}+\text{H}$)⁺ 152.0824, found: 152.0830; ^1H NMR (400 MHz, CDCl_3) δ 2.48 (t, J = 2.4 Hz, 1H), 3.55 (dd, J = 9.9, 7.4 Hz, 1H), 3.65 (dd, J = 9.9, 4.4 Hz, 1H), 4.10-4.16 (m, 1H), 4.23 (t, J = 2.4 Hz, 1H), 5.36 (dt, J = 10.3, 1.0 Hz, 2H), 5.41 (dt, J = 17.1, 1.1 Hz, 2H), 5.79 (ddd, J = 17.3, 10.3, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 58.5 (CH_2), 63.5 (CH), 71.6 (CH_2), 75.1 (CH), 79.0 (C), 119.6 (CH_2), 132.2 (CH).



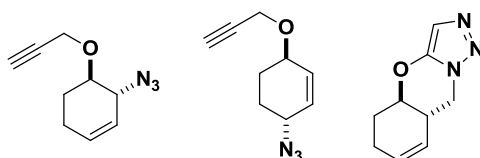
7-Vinyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine (4-106). A mixture of azides **4-105a**, **4-105b** and triazole **4-106** (18:58:24 ratio, 32 mg, 0.20 mmol) in chloroform (11 mL) under N_2 atmosphere was refluxed for 4 h. After the reaction was cooled to room temperature, solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (20-50% EtOAc/hexanes) to afford triazole **4-106** (23 mg, 72%) as a colorless oil. Triazole **4-106**: R_f = 0.45 (100% EtOAc); IR (neat) 2923, 2101 cm^{-1} ;

HRMS (ESI) m/z calculated for $C_7H_{10}N_3O$ ($M+H$)⁺ 152.0824, found: 152.0824; ¹H NMR (400 MHz, CDCl₃) δ 3.90 (dd, J = 12.1, 6.0 Hz, 1H), 4.12 (dd, J = 12.1, 4.3 Hz, 1H), 4.94 (s, 2H), 5.06 (q, J = 6.1 Hz, 1H), 5.37-5.47 (m, 2H), 5.99 (ddd, J = 17.4, 10.4, 7.2 Hz, 1H), 7.51 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 58.6 (CH), 62.5 (CH₂), 68.3 (CH₂), 120.7 (CH₂), 128.1 (CH), 130.4 (CH), 132.3 (C).



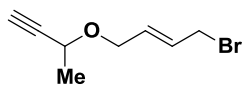
(1R*,2R*)-2-Azidocyclohex-3-enol (4-108a) and **(1R*,4R*)-4-azidocyclohex-2-enol (4-108b)**. To a solution of 7-oxabicyclo-[4.1.0]hept-2-ene (**4-107**) (3.0 g, 30 mmol) in a mixed solvent of ethanol (40 mL) and water (10 mL) was added sodium azide (2.93 g, 45.0 mmol) and ammonium chloride (2.43 g, 45.0 mmol). The resulting mixture was refluxed for 12 h. After it was cooling to room temperature, water and diethyl ether were added. After phase separation, the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (5-20% EtOAc/hexanes) to afford a mixture of azides **4-108a** and **4-108b** (82:18 ratio, 3.50 g, 81%) as a colorless oil. Pure samples of **4-108a** and **4-108b** were obtained by flash chromatography. Azide **4-108a**: R_f = 0.60 (50% EtOAc/hexanes); IR (neat) 3340, 2929, 2089 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 1.65-1.76 (m, 1H), 1.93-2.01 (m, 1H), 2.16-2.23 (m, 2H), 2.56 (br, 1H), 3.71-3.78 (m, 1H), 3.81-3.86 (m, 1H), 5.58 (dq, J = 9.9, 2.3 Hz, 1H), 5.87-5.95 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.1 (CH₂), 28.6 (CH₂), 64.3 (CH), 70.9 (CH), 123.1 (CH), 131.5 (CH). Azide **4-108b**: R_f = 0.50 (50% EtOAc/hexanes); IR (neat) 3340, 2929, 2089 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 1.47-1.57 (m, 1H), 1.57-1.66 (m, 1H), 2.00-2.16 (m, 2H), 2.80 (d, J =

5.2 Hz, 1H), 3.88-3.93 (m, 1H), 4.22 (br, 1H), 5.74 (dm, $J = 10.1$ Hz, 1H), 5.93 (dm, $J = 10.1$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 26.2 (CH_2), 29.9 (CH_2), 56.2 (CH), 65.2 (CH), 127.4 (CH), 134.7 (CH).



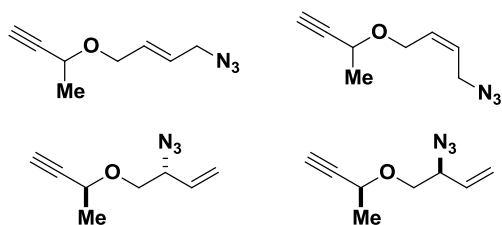
(3*R,4*R**)-3-Azido-4-(prop-2-yn-1-yloxy)cyclohex-1-ene (4-109a)**, **(3*R**,6*R**)-3-azido-6-(prop-2-yn-1-yloxy)cyclohex-1-ene (4-109b)**, and **(4*aR**,8*aS**)-5,6,8*a*,9-tetrahydro-4*aH*-benzo[*e*][1,2,3]triazolo[5,1-*b*][1,3]oxazine (4-110)**. To a solution of a mixture of azides **4-108a** and **4-108b** (900 mg, 5.00 mmol) in anhydrous DMF (20 mL) at 0 °C under N_2 atmosphere was added sodium hydride (60% in mineral oil, 240 mg, 6.00 mmol). After the resulting mixture was stirred at 0 °C for 1 h, propargyl bromide (80% w/w in toluene, 900 mg, 6.00 mmol) was added slowly. The resulting mixture was stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride. Diethyl ether was used to extract the products and the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0.5-30% EtOAc/hexanes) to afford a mixture of azides **4-109a**, **4-109b** and triazole **4-110** (1:0.05:0.15 ratio, 100 mg, 10%) as a colorless oil, a mixture of azides **4-109b**, and **4-109a** (10:1 ratio, 70 mg, 7%) as a colorless oil, unreacted starting azides **4-108a** and **4-108b** (195 mg, 22% recovered) as a colorless oil, and triazole **4-110** (250 mg, 28%) as a white solid. Azide **4-109a** (1:0.05:0.15 ratio): $R_f = 0.80$ (20% EtOAc/hexanes); IR (neat) 2877, 2095, 1084 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_9\text{H}_{12}\text{N}_3\text{O}$ ($\text{M}+\text{H}$) $^+$ 178.0980, found:

178.0977; ^1H NMR (400 MHz, CDCl_3) δ 1.63-1.75 (m, 1H), 1.99-2.08 (m, 1H), 2.09-2.27 (m, 2H), 2.48 (t, $J = 2.4$ Hz, 1H), 3.67-3.74 (m, 1H), 3.91-3.96 (m, 1H), 4.32 (dd, $J = 2.3, 1.7$ Hz, 2H), 5.56 (dq, $J = 9.9, 2.6$ Hz, 1H), 5.89-5.97 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 23.5 (CH_2), 25.3 (CH_2), 56.6 (CH_2), 61.4 (CH), 74.5 (CH), 77.4 (CH), 79.7 (C), 123.3 (CH), 131.5 (CH). (Note: After 7 days, the ratio was determined to 0.1:0.1: 1; After another 7 days, the ratio was determined to 1:1:40.) Azide **4-109b** (10:1:0 ratio): $R_f = 0.70$ (20% EtOAc/hexanes); IR (neat) 2936, 2093 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_9\text{H}_{12}\text{N}_3\text{O}$ ($\text{M}+\text{H}$) $^+$ 178.0980, found: 178.0975; ^1H NMR (400 MHz, CDCl_3) δ 1.61-1.70 (m, 2H), 2.096-2.18 (m, 2H), 2.46 (t, $J = 2.4$ Hz, 1H), 3.92-3.98 (m, 1H), 4.14-4.19 (m, 1H), 4.23 (t, $J = 2.7$ Hz, 1H), 5.85 (dt, $J = 10.2, 1.2$ Hz, 1H), 6.05 (dt, $J = 10.2, 2.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 26.0 (CH_2), 26.1 (CH_2), 55.7 (CH_2), 56.1 (CH), 71.3 (CH), 74.4 (CH), 79.9 (C), 128.4 (CH), 132.0 (CH). (After 7 days, the ratio was determined to 0.4:0.3:1; After another 7 days, the ratio was determined to 1:1:20). Triazole **4-110**: $R_f = 0.20$ (50% EtOAc/hexanes); IR (neat) 2878, 2096, 1084 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_9\text{H}_{12}\text{N}_3\text{O}$ ($\text{M}+\text{H}$) $^+$ 178.0980, found: 178.0987; ^1H NMR (400 MHz, CDCl_3) δ 1.78-1.92 (m, 1H), 2.12-2.19 (m, 1H), 2.24-2.43 (m, 2H), 3.63 (ddd, $J = 12.2, 8.8, 3.5$ Hz, 1H), 4.65 (d, $J = 8.4$ Hz, 1H), 4.91 (dm, $J = 15.2$ Hz, 1H), 5.09 (d, $J = 15.1$ Hz, 1H), 5.80-5.87 (m, 1H), 6.47 (d, $J = 10.0$ Hz, 1H), 7.43 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.1 (CH_2), 25.9 (CH_2), 59.3 (CH), 62.6 (CH_2), 76.1 (CH), 121.1 (CH), 128.5 (CH), 130.0 (CH), 130.6 (C).



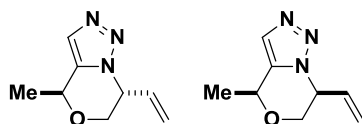
(E)-1-Bromo-4-(but-3-yn-2-yloxy)but-2-ene (4-112). To a solution of but-3-yn-2-ol (1.40 g, 20.0 mmol) in anhydrous DMF (20 mL) at room temperature under N_2 atmosphere

was added portion-wise sodium hydride (60% in mineral oil, 880 mg, 22.0 mmol). After 30 min, the above solution was slowly added to a solution of (*E*)-1,4-dibromobut-2-ene (5.56 g, 26.0 mmol) in anhydrous DMF (20 mL) at 0 °C. After the resulting mixture was stirred overnight, saturated ammonium chloride was used to quench the reaction. Diethyl ether was used to extract the product and the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0.5-2% EtOAc/hexanes) to afford bromide **4-112** (395 mg, 10%) as a colorless oil. Bromide **4-112**: R_f = 0.75 (20% EtOAc/hexanes); IR (neat) 3292, 2986, 1727 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.47 (d, J = 6.6 Hz, 3H), 2.45 (d, J = 2.0 Hz, 1H), 3.97-4.05 (m, 3H), 4.21 (qd, J = 6.6, 2.0 Hz, 2H), 4.27-4.33 (m, 1H), 5.83-5.94 (m, 1H), 5.95-6.05 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 22.0 (CH_3), 31.9 (CH_2), 64.6 (CH), 67.9 (CH_2), 73.2 (CH), 83.4 (C), 129.0 (CH), 131.2 (CH).



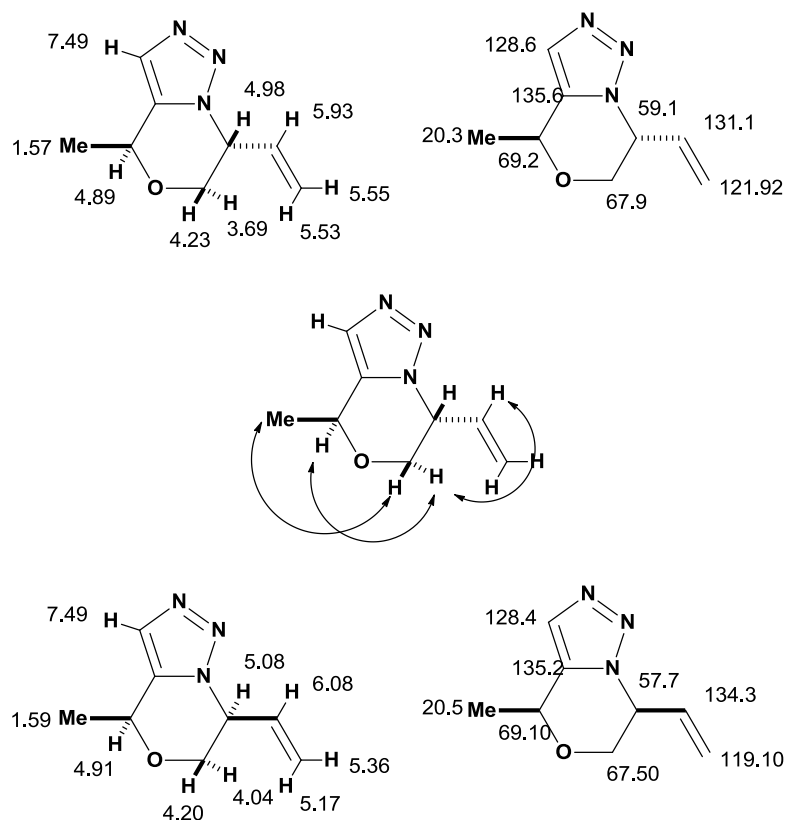
(*E*)-1-Azido-4-(but-3-yn-2-yloxy)but-2-ene (4-113a), (*Z*)-1-azido-4-(but-3-yn-2-yloxy)but-2-ene (4-113b), (*R*^{*})-3-azido-4-((*S*^{*})-but-3-yn-2-yloxy)but-1-ene (4-113c) and (*S*^{*})-3-azido-4-((*S*^{*})-but-3-yn-2-yloxy)but-1-ene (4-113d). A suspension of bromide **4-112** (820 mg, 4.00 mmol) and sodium azide (780 mg, 12.0 mmol) in DMF (15 mL) was stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride. Diethyl ether was used to extract the products and the aqueous layer was

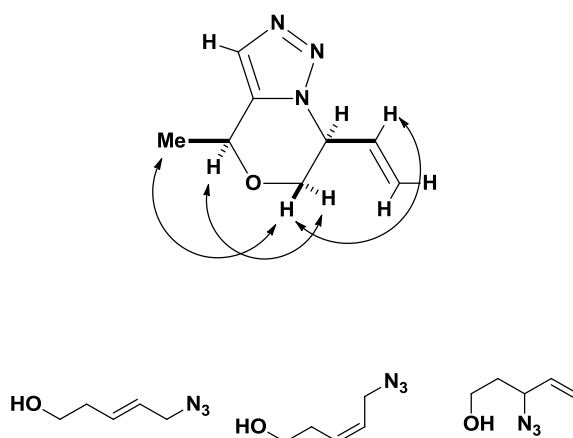
washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0.5-100% EtOAc/hexanes) to afford a mixture of azides **4-113a**, **4-113b**, **4-113c** and **4-113d** (10:0:1:1 ratio, 90 mg, 14%) as a colorless oil, triazole **4-114a** (63 mg, 10%) as a colorless oil and triazole **4-114b** (27 mg, 5%) as a colorless oil. Azides **4-113a**, **4-113b**, **4-113c**, and **4-113d** (10:0:1:1 ratio): R_f = 0.55 (10% EtOAc/hexanes); IR (neat) 3299, 2989, 2865, 2097 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_8\text{H}_{12}\text{N}_3\text{O}$ ($\text{M}+\text{H}$)⁺ 166.0980, found: 166.0979. Azide **4-113a**: ^1H NMR (400 MHz, CDCl_3) δ 1.47 (d, J = 6.6 Hz, 3H), 2.45 (d, J = 2.0 Hz, 1H), 3.77-3.83 (m, 2H), 4.02 (dd, J = 12.3, 5.3 Hz, 1H), 4.22 (qd, J = 6.6, 2.0 Hz, 1H), 4.30 (dd, J = 12.5, 4.6 Hz, 1H), 5.78-5.92 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.0 (CH₃), 52.2 (CH₂), 64.5 (CH), 68.0 (CH₂), 73.2 (CH), 83.4 (C), 126.1 (CH), 131.2 (CH). Azides **4-113c** and **4-113d** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 2.46 (d, J = 2.0 Hz, 1H), 3.41 (dd, J = 9.9, 8.1 Hz, 1H), 3.53 (dd, J = 10.0, 4.3 Hz, 1H), 5.29-5.36 (m, 1H), 5.36-5.44 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 21.9 (CH₃), 22.0 (CH₃), 63.3 (CH), 63.6 (CH), 65.5 (CH), 65.9 (CH), 70.4 (CH₂), 70.9 (CH₂), 73.4 (CH), 73.5 (CH), 83.0 (C), 83.2 (C), 119.3 (CH₂), 119.4 (CH₂), 132.35 (CH), 132.48 (CH).



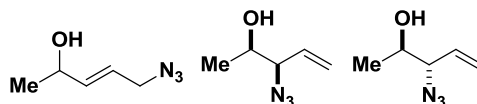
(**4S***,**7R***)-4-Methyl-7-vinyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine (**4-114a**) and (**4S***,**7S***)-4-Methyl-7-vinyl-6,7-dihydro-4H-[1,2,3]triazolo[5,1-c][1,4]oxazine (**4-114b**). Triazole **4-114a**: R_f = 0.25 (100% EtOAc/hexanes); IR (neat) 2984, 2099 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_8\text{H}_{12}\text{N}_3\text{O}$ ($\text{M}+\text{H}$)⁺ 166.0980, found: 166.0982; ^1H NMR (400 MHz, CDCl_3) δ 1.57 (d, J = 6.5 Hz, 3H), 3.69 (dd, J = 12.2, 10.0 Hz, 1H), 4.23 (dd, J = 12.2,

5.0 Hz, 1H), 4.89 (q, $J = 6.5$ Hz, 1H), 4.95-5.01 (m, 1H), 5.53 (dt, $J = 10.3, 0.7$ Hz, 1H), 5.55 (dt, $J = 17.2, 0.7$ Hz, 1H), 5.93 (ddd, $J = 17.2, 10.3, 7.8$ Hz, 1H), 7.49 (d, $J = 0.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.3 (CH_3), 59.1 (CH), 67.9 (CH_2), 69.2 (CH), 121.9 (CH_2), 128.6 (CH), 131.1 (CH), 135.6 (C). Triazole **4-114b**: $R_f = 0.20$ (100% EtOAc/hexanes); IR (neat) 2984, 2100, 1110 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_8\text{H}_{12}\text{N}_3\text{O}(\text{M}+\text{H})^+$ 166.0980, found: 166.0978; ^1H NMR (400 MHz, CDCl_3) δ 1.59 (d, $J = 6.6$ Hz, 3H), 4.05 (dd, $J = 12.1, 3.6$ Hz, 1H), 4.20 (dd, $J = 12.1, 1.5$ Hz, 1H), 4.92 (q, $J = 6.5$ Hz, 1H), 5.06-5.10 (m, 1H), 5.17 (dq, $J = 17.2, 0.6$ Hz, 1H), 5.36 (d, $J = 10.4$ Hz, 1H), 6.07 (ddd, $J = 17.0, 10.4, 6.6$ Hz, 1H), 7.50 (d, $J = 0.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.5 (CH_3), 57.7 (CH), 67.5 (CH_2), 69.1 (CH), 119.1 (CH_2), 128.4 (CH), 134.3 (CH), 135.2 (C). The following data and NOE correlations were used to assign triazoles **4-114a** and **4-114b**.

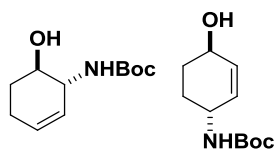




(*E*)-5-Azidopent-3-en-1-ol (4-116a), (*Z*)-5-azidopent-3-en-1-ol (4-116b) and 3-azidopent-4-en-1-ol (4-116c). Following the general procedure **III** in chapter 2, but-3-en-1-ol (7.2 g, 0.10 mol), allyl bromide (26 mL, 0.30 mol), HG-2 (206 mg, 0.330 mmol), and sodium azide (26 g, 0.40 mol) afforded a mixture of azides **4-116a**, **4-116b**, and **4-116c** (75:7:18 ratio, 5.0 g, 40%) as a colorless oil after silica gel column chromatography (5-20% EtOAc/hexanes). $R_f = 0.55$ (100% EtOAc/hexanes). Azide **4-116a**: IR (neat) 3340, 2932, 2094, 1236 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{19}\text{N}_6\text{O}_2$ ($2\text{M}+\text{H}$) $^+$ 255.1569, found: 255.1567; ^1H NMR (400 MHz, CDCl_3) δ 2.36 (q, $J = 6.5$ Hz, 2H), 3.69 (q, $J = 6.0$ Hz, 2H), 3.75 (d, $J = 6.4$ Hz, 2H), 5.60-5.69 (m, 1H), 5.73-5.83 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 35.5 (CH_2), 52.7 (CH_2), 61.7 (CH_2), 125.7 (CH), 132.6 (CH). Azide **4-116b** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 3.86 (d, $J = 7.2$ Hz, 1H). Azide **4-116c**: IR (neat) 3342, 2931, 2094, 1236 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{19}\text{N}_6\text{O}_2$ ($2\text{M}+\text{H}$) $^+$ 255.1569, found: 255.1552; ^1H NMR (400 MHz, CDCl_3) δ 1.75-1.81 (m, 2H), 2.00 (t, $J = 4.5$ Hz, 1H), 3.68-3.80 (m, 2H), 4.10 (q, $J = 7.4$ Hz, 1H), 5.31 (dt, $J = 4.1, 0.9$ Hz, 1H), 5.34 (dt, $J = 11.1, 1.0$ Hz, 1H), 5.80 (ddd, $J = 17.2, 10.2, 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 36.7 (CH_2), 59.3 (CH_2), 62.3 (CH), 118.5 (CH_2), 135.3 (CH).

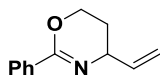


(E)-5-Azidopent-3-en-2-ol (4-118a), (2R*,3R*)-3-Azidopent-4-en-2-ol (4-118b), and (2R*,3S*)-3-Azidopent-4-en-2-ol (4-118c). Following the general procedure **III** in chapter 2, but-3-en-2-ol (7.2 g, 0.10 mol), allyl bromide (26 mL, 0.30 mol), HG-2 (206 mg, 0.330 mmol), and sodium azide (26 g, 0.40 mol) afforded a mixture of azides **4-118a**, **4-118b**, and **4-118c** (57:23:20 ratio, 5.64 g, 44%) as a colorless oil after silica gel column chromatography (5-20% EtOAc/hexanes). Azide **4-118a**: R_f = 0.45 (50% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 1.23-1.29 (m, 3H), 2.46 (br, 1H), 3.74 (d, J = 5.7 Hz, 2H), 4.27-4.37 (m, 1H), 5.64-5.75 (m, 1H), 5.77-5.86 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.3 (CH_3), 52.1 (CH_2), 67.7 (CH), 122.4 (CH), 139.5 (CH). Azide **4-118b**: IR (neat) 3374, 2977, 2096, 1244 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{19}\text{N}_6\text{O}_2$ (2M+H) $^+$ 255.1569, found: 255.1590; ^1H NMR (400 MHz, CDCl_3) δ 1.17 (d, J = 6.2 Hz, 3H), 2.53 (br, 1H), 3.63-3.70 (m, 1H), 3.74 (t, J = 7.6 Hz, 1H), 5.33-5.40 (m, 2H), 5.76 (ddd, J = 16.6, 10.6, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.2 (CH_3), 69.2 (CH), 71.7 (CH), 120.6 (CH_2), 132.4 (CH). Azide **4-118c**: ^1H NMR (400 MHz, CDCl_3) δ 1.17 (d, J = 6.3 Hz, 3H), 2.20 (br, 1H), 3.80-3.85 (m, 1H), 3.86-3.91 (m, 1H), 5.38 (d, J = 17.1 Hz, 1H), 5.44 (d, J = 10.1 Hz, 1H), 5.84 (ddd, J = 17.2, 10.3, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 18.5 (CH_3), 68.9 (CH), 70.5 (CH), 121.2 (CH_2), 131.5 (CH).

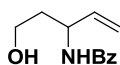


***tert*-Butyl ((1*R**,6*R**)-6-hydroxycyclohex-2-en-1-yl)carbamate (4-119)** and ***tert*-butyl ((1*R**,4*R**)-4-hydroxycyclohex-2-en-1-yl)carbamate (4-120)**. To a solution of azide **4-108a** and **4-108b** (82:18 ratio, 280 mg, 2.00 mmol) in methanol (20 mL) was added tin(II) chloride (760 mg, 4.00 mmol). After the resulting mixture was stirred for 11 h, dioxane (20 mL) and water (5 mL) were added, followed by the addition of (Boc)₂O (900 mg, 4.00 mmol), sodium carbonate (864 mg, 8.00 mmol) and catalytic amount of DMAP. The resulting mixture was stirred overnight before the addition of 1 M aqueous hydrochloride solution to acidify the solution. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (5-20% EtOAc/hexanes) to afford carbamate **4-119** (250 mg, 59%) as a colorless oil and carbamate **4-120** (70 mg, 17%) as a colorless oil. Carbamate **4-119**: *R_f* = 0.30 (50% EtOAc/hexanes); IR (neat) 3323, 2979, 1681, 1517 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₁H₁₉NO₃Na (M+Na)⁺ 236.1263, found: 236.1261; ¹H NMR (400 MHz, CDCl₃) δ 1.45 (s, 9H), 1.59-1.72 (m, 1H), 1.91-1.97 (m, 1H), 2.03-2.20 (m, 2H), 3.63 (ddd, *J* = 10.7, 7.3, 3.5 Hz, 1H), 3.88 (br, 1H), 4.05 (br, 1H), 4.78 (d, *J* = 6.3 Hz, 1H), 5.40 (d, *J* = 9.5 Hz, 1H), 5.80 (d, *J* = 7.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 23.9 (CH₂), 28.4 (CH₃), 28.9 (CH₂), 55.0 (CH), 73.0 (CH), 80.2 (C), 125.6 (CH), 130.6 (CH), 157.3 (C). Carbamate **4-120**: *R_f* = 0.20 (50% EtOAc/hexanes); IR (neat) 3316, 2930, 1680, 1525, 1168 cm⁻¹; HRMS (ESI) *m/z* calculated for C₁₁H₁₉NO₃Na (M+Na)⁺ 236.1263, found: 236.1249; ¹H NMR (400 MHz, CDCl₃) δ 1.46 (s, 9H), 1.53-1.63 (m, 2H), 2.05-2.18 (m, 2H), 4.24 (br, 2H), 4.48 (br, 1H), 5.72 (d, *J* = 10.1 Hz, 1H), 5.83 (d, *J*

= 10.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 28.1 (CH_2), 28.4 (CH_3), 30.9 (CH_2), 46.4 (CH), 66.0 (CH), 79.5 (C), 131.0 (CH), 132.9 (CH), 155.2 (C).



2-Phenyl-4-vinyl-5,6-dihydro-4H-1,3-oxazine (4-100). To a refluxing solution of a mixture of azides **4-116a**, **4-116b**, and **4-116c** (210 mg, 1.65 mmol) and benzaldehyde (175 mg, 1.65 mmol) in 1,2-dichloroethane (16 mL) under N_2 atmosphere, was slowly added $\text{BF}_3 \cdot \text{OEt}_2$ (467 mg, 3.3 mmol). The resulting mixture was refluxed overnight. Saturated ammonium chloride was used to quench the reaction and dichloromethane was used to extract the product. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (2-10% EtOAc/hexanes) to afford oxazine **4-100** (70 mg, 23%) as a colorless oil. Oxazine **4-100**: R_f = 0.70 (20% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 1.76-1.85 (m, 1H), 2.09-2.18 (m, 1H), 4.20-4.26 (m, 1H), 4.32-4.39 (m, 2H), 5.24 (dt, J = 10.3, 1.6 Hz, 1H), 5.30 (dt, J = 17.1, 1.7 Hz, 1H), 6.02 (ddd, J = 17.1, 10.3, 5.2 Hz, 1H), 7.35-7.47 (m, 3H), 7.96-8.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 27.0 (CH_2), 53.0 (CH), 63.2 (CH_2), 115.2 (CH_2), 127.1 (CH), 128.0 (CH), 130.4 (CH), 134.0 (C), 140.2 (CH), 155.1 (C).



N-(5-Hydroxypent-1-en-3-yl)benzamide (4-101). To a solution of oxazine **4-100** (90 mg, 0.5 mmol) in a mixed solvent of acetone (5 mL) and water (5 mL), was added potassium carbonate (350 mg, 2.5 mmol). The resulting mixture was stirred overnight. 1N

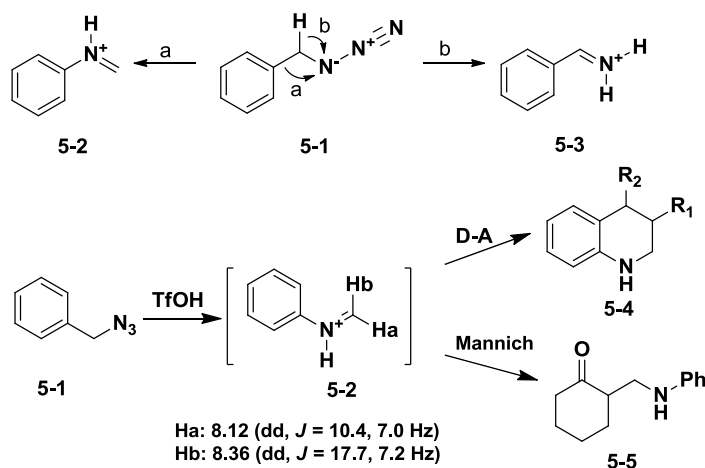
HCl solution was used to neutralize the solution, and ethyl acetate was used to extract the product. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (5-100% EtOAc/hexanes) to afford alcohol **4-101** (12 mg, 12%) as a colorless oil. Alcohol **4-101**: R_f = 0.30 (100% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 1.60-1.68 (m, 1H), 2.04-2.13 (m, 1H), 3.55 (br, 1H), 3.69-3.79 (m, 2H), 4.89-4.97 (m, 1H), 5.25 (ddd, J = 10.5, 1.6, 0.9 Hz, 1H), 5.32 (ddd, J = 17.3, 1.7, 0.9 Hz, 1H), 5.97 (ddd, J = 17.3, 10.5, 5.1 Hz, 1H), 6.58 (br-d, J = 7.4 Hz, 1H), 7.43-7.50 (m, 2H), 7.51-7.57 (m, 1H), 7.79-7.85 (m, 2H).

CHAPTER 5

THE REORGANIZATION OF ALLYLIC AZIDE TO AZADIENE

5.1 Introduction

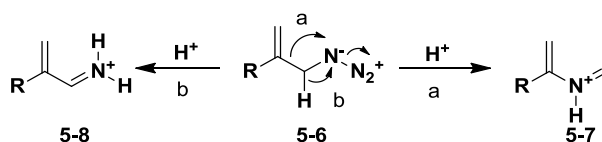
Under strong acidic conditions, there are two possible migrating groups in benzyl azide **5-1**; the migration of hydrogen atom leads to the formation of protonated benzylimine **5-3** (route b), and the migration of phenyl group yields a protonated 2-azadiene **5-2** (route a) (Scheme 110). In 1997, Pearson and coworkers reported the reorganization of benzyl azide to 2-azadiene and its subsequent Diels-Alder reactions to tetrahydroquinoline **5-4**.¹⁵⁵ A year later, our group reported the same reorganization and the following Mannich reactions to β -amino ketone **5-5**.¹⁵⁶⁻¹⁵⁸ Diels-Alder reactions of intermediate **5-2** with indoles or enamides have been reported recently.^{159,160}



Scheme 110. Reorganization involving benzyl azides.

Based on our discoveries involving allylic azides, we theorized that the allylic azide could undergo a similar reorganization (Scheme 111). Similar to benzyl azide, the migration

of vinyl group would give protonated 2-azadiene **5-7**, and the migration of H group leads to the formation of protonated 1-azadiene **5-8**. Such reorganization could potentially have more synthetic applications than the one involving benzyl azide, which has limited its utility owing to the necessary presence of phenyl ring.



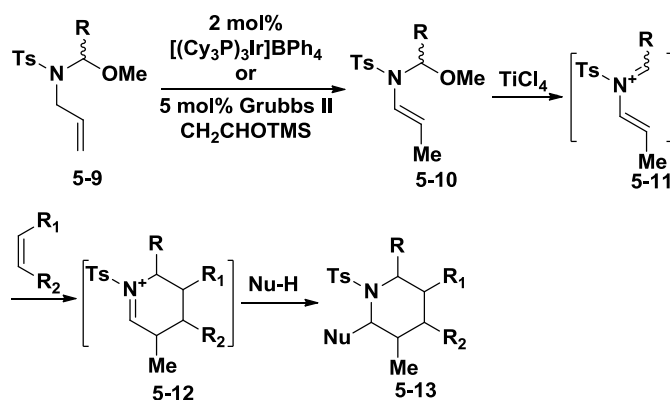
Scheme 111. Reorganization involving allylic azides.

1-Azadiene has been considered a π -electron deficient diene system due to its low reactivity with electron-poor dienophiles in the normal Diels-Alder reaction.^{161,162} Based on a rudimentary calculation of bond cleavage and formation by Jung and coworkers,¹⁶³ 2-azadiene only has two C=C bond cleavages and four C-C bond formations, which is the same as butadiene, thus it was preferred in the Diels-Alder reaction by 20 kcal/mol over 1-azadiene, which only has C=C and C=N bond cleavages, and 2 C-C and 2 C-N bond formations. This is probably a result of the relatively weak C-N bond (C-N 73 kcal/mol vs C-C 86 kcal/mol; C=N 147 kcal/mol vs C=C 146 kcal/mol). Bachrach and coworkers calculated the relative activation and reaction energy for these dienes,¹⁶⁴ and they found by any methods used that 1-azadiene always has higher activation energy and lower reaction energy over 2-azadiene, which has similar numbers to butadiene.

Thus the generated protonated 1-azadiene (**5-3** and **5-8**) and 2-azadiene (**5-2** and **5-7**), from either benzyl azide or allylic azide under strong acidic conditions, are different from what we discussed about above, because the nitrogen atom is protonated. Hence, their behavior and performance in organic synthesis may be different.

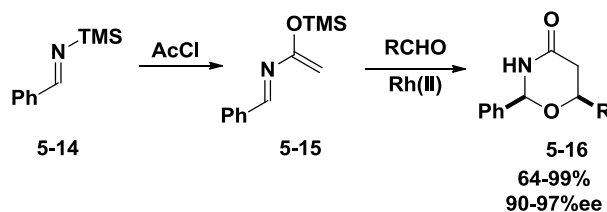
To the best of our knowledge, there are no general methods to prepare mono-substituted 1-azadiene and 2-azadiene. Herein, we are only focusing on the recent development of 2-azadiene with fewer than two substituents.

Recently, Scott and coworkers reported the generation of a 2-azadiene precursor by the migration of the double bond along the alkyl chain (Scheme 112).¹⁶⁵ Upon activation by a Lewis acid, 2-azadiene iminium ion **5-11** was generated and reacted with electron-neutral dienes to produce substituted piperidines **5-13**.



Scheme 112. Scott's preparation of 2-azadiene and reactions.

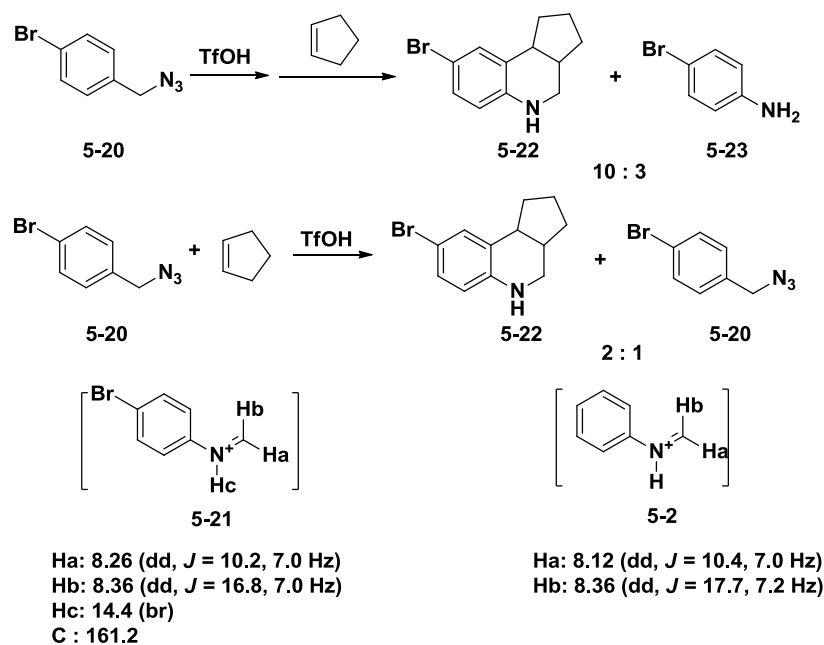
Hashimoto and coworkers reported the Rh(II)-catalyzed enantioselective Diels-Alder reaction of 2-azadiene, which was prepared from imine and acyl chloride via [1,3]-Brook rearrangement (Scheme 113).¹⁶⁶ This reaction can tolerate a wide range of aliphatic and aromatic aldehydes with either electron-donating or electron-withdrawing substituents.



Scheme 113. Rh(II)-catalyzed enantio-selective Diels-Alder reaction of 2-azadiene.

5.2 Results and discussion

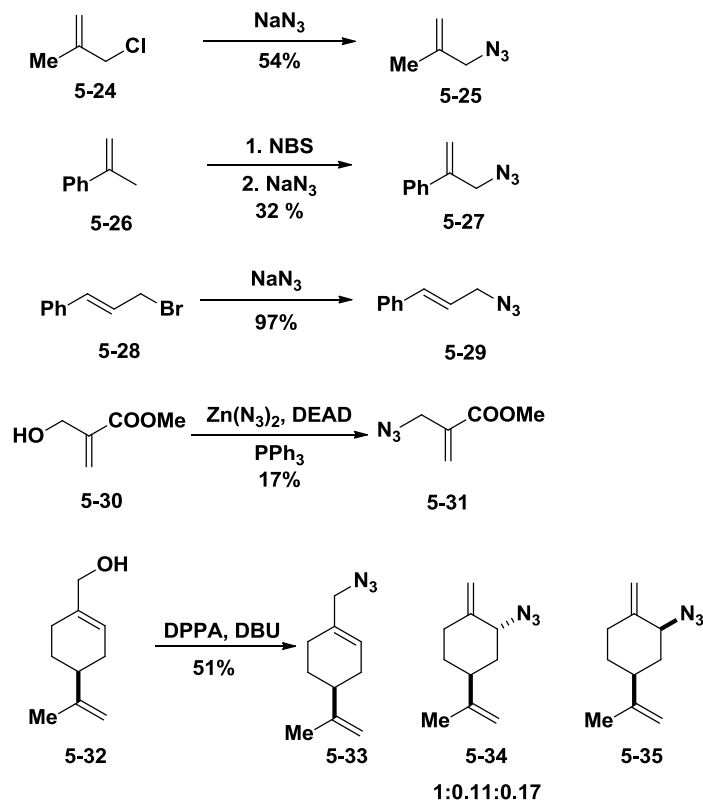
Following the reported procedure,¹⁵⁵ we first tried to achieve the reorganization of benzyl azide **5-20** (Scheme 114). When 4-bromobenzyl azide **5-20** was treated with triflic acid, a stable 2-azadiene intermediate **5-21** was generated; the spectral data of the obtained material compares to that of the reported intermediate **5-2**. We conducted the following Diels-Alder reaction with cyclopentene using two types of addition sequence: the early and late addition of cyclopentene to 2-azadiene **5-21**. In the case of late addition sequence, hydrolyzed product of 2-azadiene intermediate, 4-bromoaniline **5-23**, was obtained. Unreacted benzyl azide was recovered for the reaction involving early addition sequence, which may be a result of the initial reaction of triflic acid with cyclopentene to form cyclopentyl carbocation, instead of the reaction with benzyl azide to generate **5-21**.



Scheme 114. Reorganization of 4-bromobenzyl azide.

Preparation of allylic azides. Five allylic azides were prepared by either azide displacement or Mitsunobu reaction (Scheme 115). When perillyl alcohol was converted to

allylic azides, a mixture of **5-33**, **5-34**, and **5-35** in a 1:0.11:0.17 ratio was obtained. Compound **5-35** with the axial azide group is more stable than **5-34** due to A^{1,3} strain generated from azide and vinyl hydrogen.



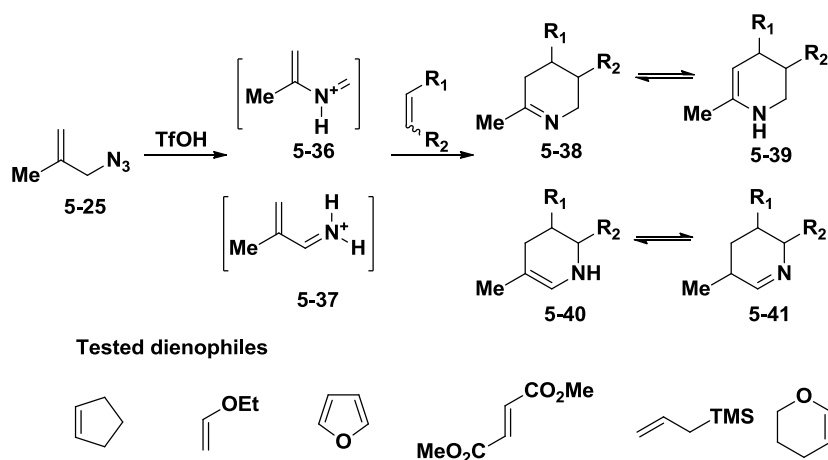
Scheme 115. Preparation of allylic azides.

When allylic azide **5-25** was treated with triflic acid, intermediates **5-36** and **5-37** may be generated (Scheme 116). They can react with electron-rich or electron-deficient dienophiles to produce tetrahydropyridines **5-38** and **5-40**, which may isomerize to **5-39** and **5-41**, respectively, under acidic conditions. This equilibration is in the favor of the stable thermodynamic product based on their conformations.

A number of dienophiles with electron-donating, electron-neutral, and electron-withdrawing substituents were tested and did not yield cycloadducts. We also investigated the same reaction at different temperatures, solvents, addition sequences, and bases without

success. A similar result was observed when triethylamine and 2,6-di-*t*-butyl 4-methyl pyridine were added in an attempt to make the reaction conditions less acidic. The spectral data of intermediate **5-36** or **5-37** was also acquired; however, it did not match with our desired intermediate. It also indicated the existence of one intermediate without the starting allylic azide. Diels-Alder cycloaddition with different dienes yielded a complicated mixture, and no useful information could be deduced from these reactions.

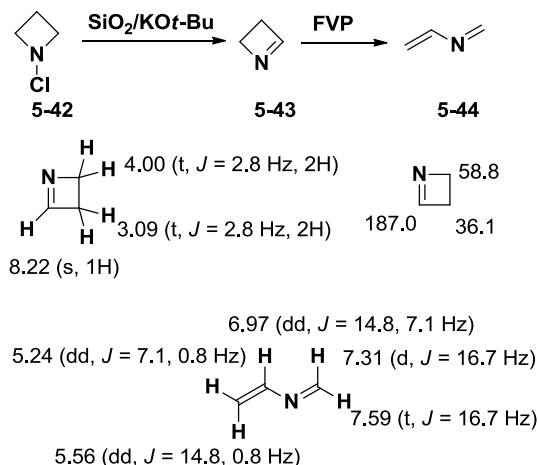
We also tested allylic azide **5-27** for this conversion, and it was more complex than azide **5-25** because the spectrum of intermediate showed the existence of two intermediates, one of which resembles an intermediate from **5-25** and the other one resembles **5-37**.



Scheme 116. Diels-Alder reaction of reorganized allylic azide **5-25**.

Fortunately, we came across one paper by Denis and coworkers,¹⁶⁷ in which they reported the synthesis of 1-azetine and its thermal ring opening to 2-azabutadiene (Scheme 117). They also mentioned that 1-azetine polymerizes in a few seconds in sealed degassed tubes at 20 °C, and its half-life in CFCl₃ solution is 3 days in the presence of hydroquinone. If trace amounts of oxygen or acid were present, polymerization occurred rapidly. The structure of 1-azetine was confirmed by LAH reduction and cyanide attack, and the ¹H NMR spectrum of 2-azabutadiene was acquired at -60 °C. Its polymerization in a dilute solution only takes a

few minutes at 25 °C. From this data, it can be inferred that 2-azabutadiene is less stable than 1-azetine.



Scheme 117. Preparation of 2-azabutadiene.

We then considered if the similar electrocyclization did occur in our system. First, we compared our data with reported data¹⁶⁷ (Scheme 117 and Figure 128) and found that the chemical shift pattern of proton and carbon NMR, as well as coupling constants, are similar to the reported data of 1-azetine.¹⁶⁷ This comparison suggested that electrocyclization could occur after the initial reorganization of the allylic azides.

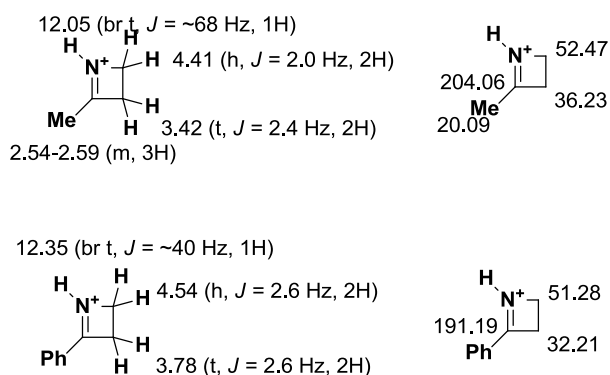
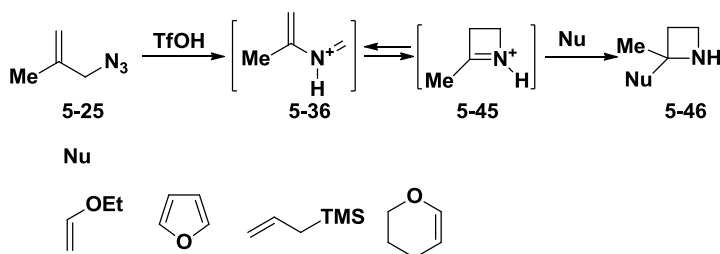


Figure 128. ¹H and ¹³C NMR data of intermediates.

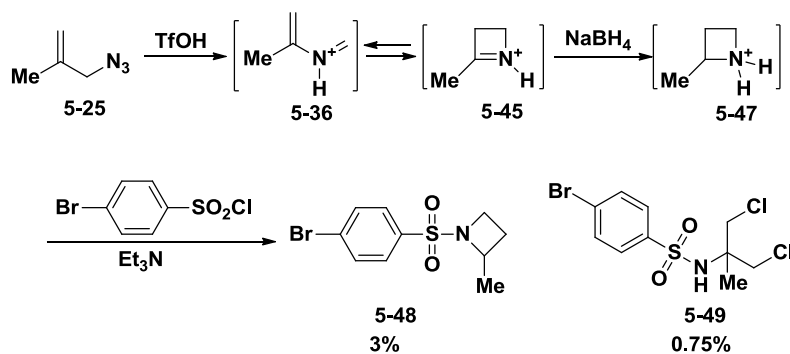
Upon the electrocyclization of 2-azadiene **5-36**, the generated intermediate **5-45** should react with strong nucleophiles to produce azetidine **5-46** (Scheme 118). With this in

mind, we re-examined our results, and did not find evidence for the existence of **5-46** in the crude products. Stronger conditions should be utilized to achieve this conversion. Furthermore, the azetine **5-45** did not react with furan to afford Diels-Alder adducts.



Scheme 118. Re-examination of our results.

In order to further confirm this, we tried to reduce the 1-azetine **5-45** to azetidine **5-47**, hoping the subsequent sulfonylation could provide us the protected azetidine **5-48** (Scheme 119). We expected to get a usable crystal for X-ray crystallography to confirm the structure. Unfortunately, we obtained a mixture of **5-48** and **5-49**, the latter being confirmed by X-ray (Figure 129), in a very low yield with a 4:1 ratio.



Scheme 119. Reduction of azetine.

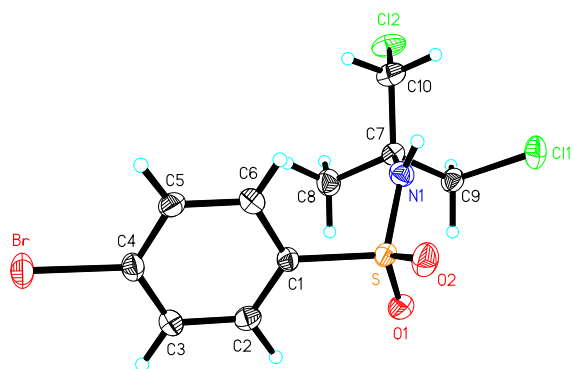


Figure 129. ORTEP representation of **5-49**.

We proposed a mechanism for the formation of compound **5-49** (Figure 130). The internal nitrogen of azide **5-25** could be protonated by triflic acid, and the generated trifluomethylsulfonate counter ion could attack dichloromethane to produce a chloride ion. Aziridine **5-51** could be generated upon the attack of chloride on **5-50** and with the concomitant extrusion of nitrogen gas. The subsequent chloride attack might afford amine **5-52**, whose subsequent sulfonylation would give **5-49**.

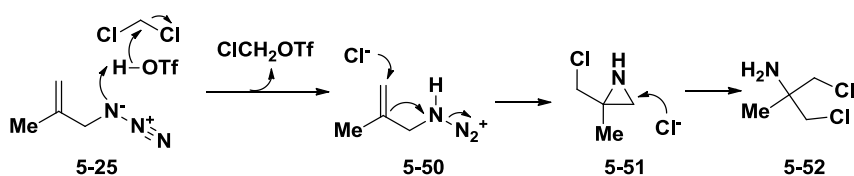
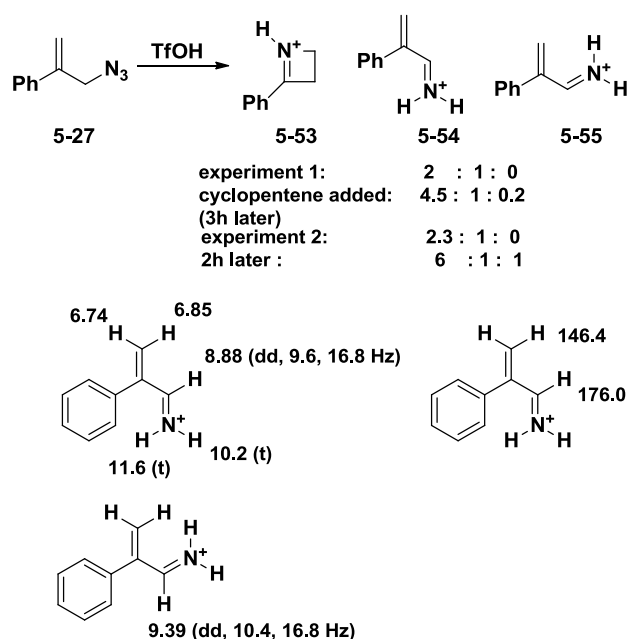


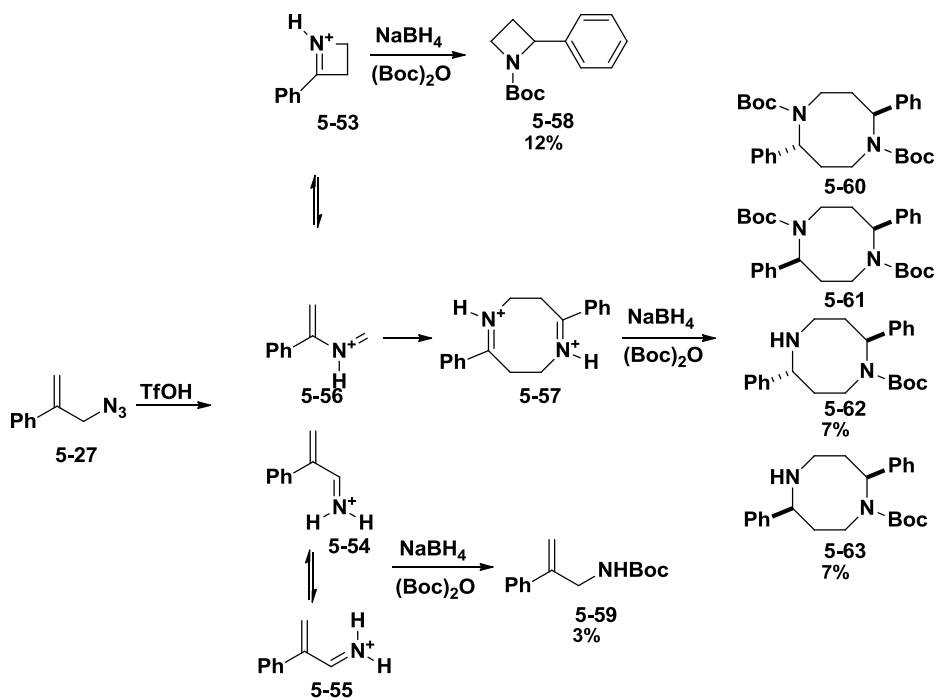
Figure 130. Proposed mechanism for the formation of **5-49**.

Allylic azide **5-27** was treated with triflic acid, and **5-54** was obtained along with azetidine **5-53**, whose spectral data is shown in Figure 128. Although the initial ratio of **5-53** and **5-54** is 2:1, *s*-cis **5-54** was slowly transferred with time to *s*-trans **5-55** (Scheme 120). The relative stereochemistry of *s*-cis **5-54** was confirmed by 2D NMR.



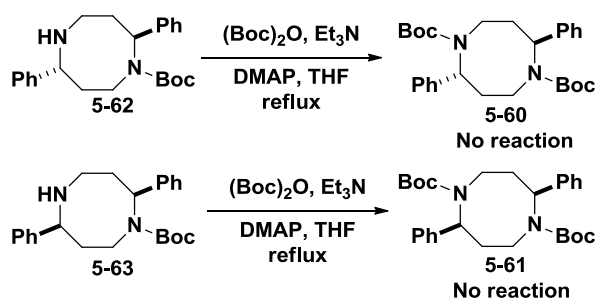
Scheme 120. Reorganization of azide **5-27**.

In order to further confirm the structure of azetidine **5-53**, we treated the mixture of **5-53** and **5-54** with sodium borohydride, followed by the subsequent Boc protection, and this reaction afforded four compounds (Scheme 121). The existence of **5-59**, whose spectral data matched reported data,¹⁶⁸ might indicate the existence of the proposed intermediate **5-54** or **5-55**. Another possibility is the direct reduction of azide **5-27** to **5-59**. The presence of **5-62** and **5-63**, whose structures were confirmed by 2D NMR, indicated that dimerization occurred before electrocyclization.



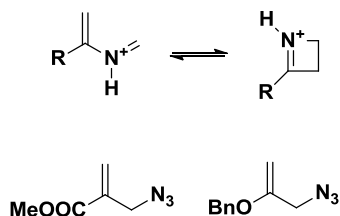
Scheme 121. Reduction and protection of azide **5-27** intermediates.

The comparison of intermediate **5-53** and **5-57** indicated that their spectral data should be very similar. The coupling constant of two methylene groups in **5-57** should be larger because the ring system of **5-57** is more flexible than **5-53**. Currently, we only have the NMR data of one compound and it is difficult to conclude whether it is **5-58**, **5-60** or **5-61**. HRMS analysis did not provide any useful information. We attempted to incorporate the second Boc group in the compounds **5-62** and **5-63** to get **5-60** and **5-61** (Scheme 122). Thus, we could compare the spectral data of **5-62** and **5-63** with the data on hand to identify them; and further we can know if the reaction is the dimerization or electrocyclization. Unfortunately, the reaction, which is similar to reduction-protection shown in Scheme 121, did not work out as planned. Retrospectively, we should get **5-60** or **5-61** if the compound on hand is **5-60** or **5-61**. This further enhances the probability of **5-58** in this reaction. Additional experiments need to be conducted to confirm this conversion.



Scheme 122. Boc protection of mono-protected dimer.

Currently we speculated that an equilibrium exists between 1-azetine and 2-azadiene. In order to inhibit the electrocyclization to 1-azetine and push 2-azadiene forward for Diels-Alder reaction, we plan to add electron-donating or electron-withdrawing groups to allylic azides to test which kind of group is better for this reorganization (Scheme 123).

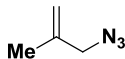


Scheme 123. Future directions.

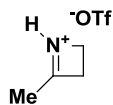
5.3 Conclusion

In this chapter, attempts were made to reorganize allylic azide for Diels-Alder reaction. Initial studies indicated that there may be electrocyclization for protonated 2-azadiene to 1-azetine, after the comparison of our intermediates with reported data. However, this conversion needs to be further confirmed.

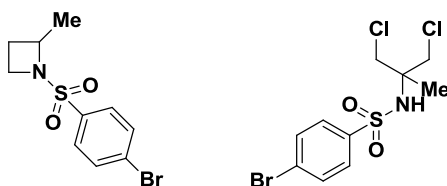
5.4 Experimental data



3-Azido-2-methylprop-1-ene (5-25). To a solution of 3-chloro-2-methylprop-1-ene (9.06 g, 0.10 mol) in DMF (50 mL) was added sodium azide (13 g, 0.20 mol) portionwise. The resulting mixture was stirred overnight, and water was used to quench the reaction. Diethyl ether was used to extract the product and the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated at 1 atm atmospheric pressure. The residue was purified by reductive distillation (55-65 °C/110 mmHg) to afford azide **5-25** (5.2 g, 54%) as a colorless oil. Azide **5-25**: ^1H NMR (400 MHz, CDCl_3) δ 1.82 (s, 3H), 3.73 (s, 2H), 4.99-5.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.2 (CH_3), 57.2 (CH_2), 114.3 (CH_2), 139.5 (C); ^1H NMR (400 MHz, CD_2Cl_2) δ 1.82 (t, $J = 1.1$ Hz, 3H), 3.76 (s, 2H), 5.01 (q, $J = 1.1$ Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 19.9, 57.1, 113.7, 139.9.

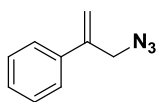


4-Methyl-2,3-dihydroazet-1-ium trifluoromethanesulfonate (5-45). To a solution of azide **5-25** (60 mg, 0.62 mmol) in CD_2Cl_2 (1 mL) under N_2 atmosphere at 0 °C was added triflic acid (116 mg, 0.740 mmol) slowly. After the addition, ice bath was removed and the resulting mixture was continued to stir for 30 min before NMR spectra were acquired. ^1H NMR (400 MHz, CD_2Cl_2) δ 2.54-2.59 (m, 3H), 3.42 (t, $J = 2.4$ Hz, 2H), 4.41 (h, $J = 2.0$ Hz, 2H), 12.05 (br t, $J = \sim 68$ Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 20.1 (CH_3), 36.2 (CH_2), 52.5 (CH_2), 119.9 (q, $J = 316$ Hz, 1C), 124.6, 204.1 (C).



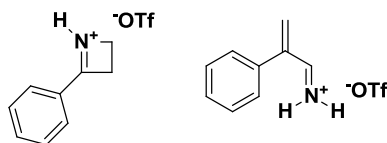
1-((4-Bromophenyl)sulfonyl)-2-methylazetidine (5-48) and **4-bromo-N-(1,3-dichloro-2-methylpropan-2-yl)benzenesulfonamide (5-49)**. To a solution of azide **5-25** (135 mg, 1.39 mmol) in CH_2Cl_2 (3 mL) under N_2 atmosphere at -78°C was added triflic acid (250 mg, 1.67 mmol) slowly. Gas emission was observed and the white solid was gradually formed as the reaction is stirred. After 20 min at -78°C , cyclopentene (0.4 mL) was added slowly and the resulting mixture was warmed slowly to room temperature (NMR showed no reaction). The mixture was cooled to -78°C , and sodium borohydride (120 mg, 3.2 mmol) was added. After the reaction was warmed to room temperature, methanol was used to quench the reaction. Dichloromethane and water were added to the reaction mixture. After separation, the aqueous layer was washed with dichloromethane three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. To the residue and triethylamine (303 mg, 3.00 mmol) in dichloromethane (15 mL) at room temperature was added 4-bromobenzene sulfonyl chloride (360 mg, 1.4 mmol) slowly. The resulting mixture was stirred overnight. 1M HCl was used to quench the reaction. Dichloromethane was used to extract the product, and the aqueous layer was washed with dichloromethane three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (1-15% EtOAc/hexanes) to afford a mixture of **5-48** and **5-49** (4:1 ratio, 16 mg, 3% + 0.75%) as a powder. Amine **5-48**: $R_f = 0.30$ (20% EtOAc/hexanes); IR (neat) 2971, 1342, 1160 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{10}\text{H}_{12}\text{BrNO}_2\text{Na}$ ($2\text{M}+\text{Na}$) $^+$ 311.9670, found: 311.9688; ^1H NMR (400 MHz, CDCl_3) δ 1.43 (d, $J = 6.2$ Hz, 3H), 1.88-

1.98 (m, 1H), 2.01-2.10 (m, 1H), 3.53 (q, $J = 8.7$ Hz, 2H), 3.67-3.76 (m, 1H), 3.97-4.07 (m, 1H), 7.65-7.81 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 22.3 (CH_3), 24.1 (CH_2), 47.6 (CH_2), 60.6 (CH), 128.1 (C), 129.7 (CH), 132.4 (CH), 134.4 (C). Amine **5-49** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.38 (s, 3H), 3.62 (d, $J = 11.3$ Hz, 2H), 3.78 (d, $J = 11.3$ Hz, 2H), 5.09 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.6 (CH_3), 49.0 (CH_2), 59.5 (C), 128.5 (CH), 132.5 (CH).

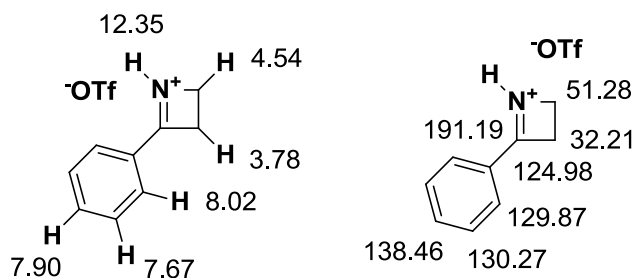


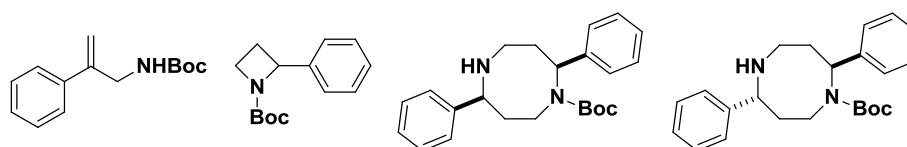
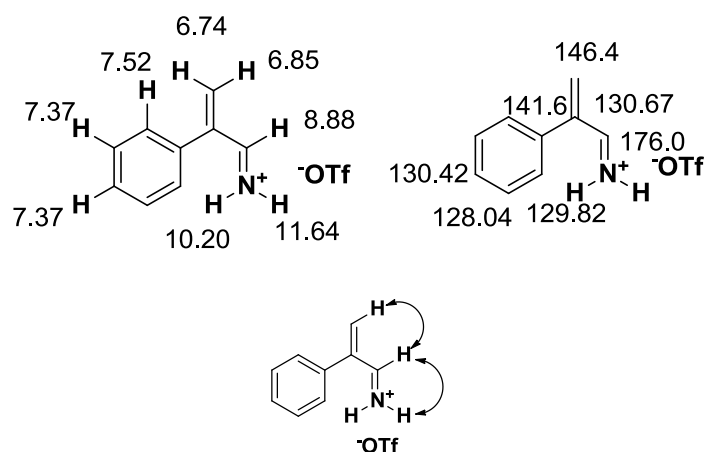
(3-Azidoprop-1-en-2-yl)benzene (5-27). A suspension of α -methylstyrene (50 g, 0.42 mol) and *N*-bromosuccinimide (46 g, 0.26 mol) in carbon tetrachloride (20 mL) was rapidly heated to 160-170 °C until the solids were dissolved. The reaction is very exothermic and the released heat energy assisted to keep the reaction mixture in the refluxing condition for 8 h. After the mixture was allowed to cool to room temperature, the precipitates were filtered out and washed with carbon tetrachloride. The filtrate was concentrated to afford a mixture of α -methylstyrene, (3-bromoprop-1-en-2-yl)benzene, and (1-bromoprop-1-en-2-yl)benzene (1:1:0.6 ratio, 75 g). To a solution of the above residue (37.5 g) in DMF (60 mL) was added slowly sodium azide (16.3 g, 0.25 mol) at room temperature. The resulting mixture was stirred overnight and diethyl ether and were added to the mixture. After separation, the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (1-5% EtOAc/hexanes) to afford azide **5-27** (6.64 g, 32%) as a colorless oil. Azide **5-27**: $R_f = 0.30$ (1% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 4.22 (s, 2H), 5.36-5.41 (m, 1H), 5.65 (s, 1H),

7.34-7.43 (m, 2H); 7.47-7.53 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 55.0 (CH_2), 116.2 (CH_2), 126.0 (CH), 128.3 (CH), 128.6 (CH), 138.1 (C), 141.8 (C).



4-Phenyl-2,3-dihydroazet-1-ium trifluoromethanesulfonate (5-53) and **2-phenylprop-2-en-1-iminium trifluoromethanesulfonate (5-54)**. To a solution of azide **5-27** (165 mg, 1.04 mmol) in CD_2Cl_2 (1.5 mL) under N_2 atmosphere at 0 °C was added triflic acid (187 mg, 1.24 mmol) slowly. After the addition, ice bath was removed and the resulting green mixture was continued to stir for 20 min before NMR spectra were acquired. Iminium salts **5-53** and **5-54** (2:1 ratio). Iminium salt **5-53**: ^1H NMR (400 MHz, CD_2Cl_2) δ 3.78 (t, J = 2.6 Hz, 2H), 4.54 (t, J = 2.6 Hz, 2H), 7.67 (t, J = 7.6 Hz, 2H), 7.90 (t, J = 7.6 Hz, 1H), 8.02 (t, J = 7.8 Hz, 2H), 12.35 (br t, J = ~40 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 32.2 (CH_2), 51.3 (CH_2), 119.8 (q, J = 316 Hz, 1C), 125.0 (C), 129.9 (CH), 130.3 (CH), 138.5 (CH), 191.2 (C). Iminium salt **5-54**: ^1H NMR (400 MHz, CD_2Cl_2) δ 6.74 (s, 1H), 6.85 (s, 1H), 7.32-7.43 (m, 3H), 7.47-7.57 (m, 2H), 8.88 (dd, J = 18.8, 9.7 Hz, 1H), 10.20 (br t, J = ~55 Hz, 1H), 11.64 (br t, J = ~55 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 128.0 (CH), 129.8 (CH), 130.4 (CH), 130.7 (C), 141.6 (C), 146.4 (CH_2), 176.0 (CH). The following data and NOE correlations were used to assign iminium salts **5-53** and **5-54**.

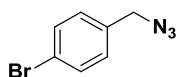
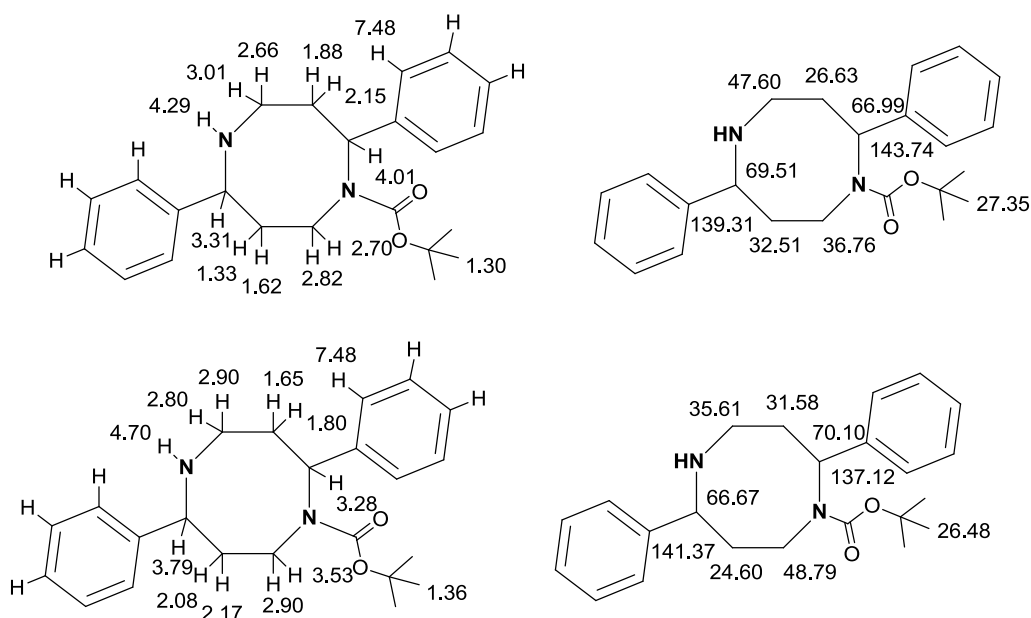




***tert*-Butyl (2-phenylallyl)carbamate (5-59), *tert*-butyl 2-phenylazetididine-1-carboxylate (5-58), (2*S**,6*S**)-*tert*-butyl 2,6-diphenyl-1,5-diazocane-1-carboxylate (5-63) and (2*S**,6*R**)-*tert*-butyl 2,6-diphenyl-1,5-diazocane-1-carboxylate (5-62).** To a solution of azide **5-27** (159 mg, 1.00 mmol) in CH₂Cl₂ (6 mL) under N₂ atmosphere at 0 °C was added triflic acid (193 mg, 1.29 mmol) slowly. The resulting green reaction was stirred for 10 min before sodium borohydride (190 mg, 5.00 mmol) was added. After the mixture was warmed to room temperature, methanol (1 mL) was added slowly. The resulting mixture was continued to stir for 2.5 h, and aqueous sodium hydroxide (3 M, 1 mL, 3 mmol) was added before the addition of (Boc)₂O (660 mg, 3.00 mmol) and catalytic amount of DMAP were added. The resulting mixture was heated to reflux for 3.5 h. After the reaction was cooled to room temperature, ethyl acetate and water were added to the reaction mixture. After separation, the aqueous layer was washed with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and

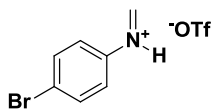
concentrated. The residue was purified by silica gel column chromatography (0.5-5% EtOAc/hexanes) to afford amine **5-59** (7 mg, 3%) as a colorless oil, amine **5-58** (27 mg, 12%) as a colorless oil, amine **5-63** (or **5-62**) (12 mg, 3%) as a colorless oil and amine **5-62** (or **5-63**) (12 mg, 3%) as a colorless oil. Amine **5-59**: R_f = 0.35 (20% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 1.46 (s, 9H), 4.22 (d, J = 5.4 Hz, 2H), 4.67 (br, 1H), 5.24-5.27 (m, 1H), 5.45 (s, 1H), 7.30-7.40 (m, 3H), 7.45 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 28.4 (CH_3), 44.4 (CH_2), 79.5 (C), 113.2 (CH_2), 126.2 (CH), 127.9 (CH), 128.5 (CH), 138.7 (C), 144.9 (C), 155.7 (C). Amine **5-58**: R_f = 0.30 (20% EtOAc/hexanes); IR (neat) 2975, 1697 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{Na}$ ($2\text{M}+\text{Na}$) $^+$ 256.1313, found: 256.1312; ^1H NMR (400 MHz, CDCl_3) δ 1.35 (br, 9H), 2.11-2.20 (m, 1H), 2.59-2.69 (m, 1H), 4.02 (t, J = 7.6 Hz, 2H), 5.20 (t, J = 7.6 Hz, 1H), 7.26-7.32 (m, 1H), 7.36-7.40 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 25.4 (CH_2), 28.3 (CH_3), 46.6 (CH), 64.3 (CH_2), 79.4 (C), 125.9 (CH), 127.3 (CH), 128.4 (CH), 142.6 (C), 156.6 (C). Amine **5-63** (or **5-62**): R_f = 0.50 (100% EtOAc/hexanes); IR (neat) 3357, 2974, 1699 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 367.2386, found: 367.2358; $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 389.2205, found: 389.2200; ^1H NMR (500 MHz, CDCl_3) δ 1.30 (s, 9H), 1.29-1.38 (m, 1H), 1.59-1.66 (m, 1H), 1.88 (pentet, J = 9.0, 4.8 Hz, 1H), 2.15 (qd, J = 8.0, 1.8 Hz, 1H), 2.63 (q, J = 8.0 Hz, 1H), 2.66-2.73 (m, 1H), 2.77-2.86 (m, 1H), 3.01 (t, J = 6.8 Hz, 1H), 3.31 (dd, J = 8.3, 4.8 Hz, 1H), 4.01 (t, J = 8.1 Hz, 1H), 4.29 (br, 1H), 7.17-7.31 (m, 8H), 7.47-7.50 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 26.6 (CH_2), 27.4 (3CH_3), 32.5 (CH_2), 36.8 (CH_2), 47.6 (CH_2), 67.0 (CH), 69.5 (CH), 77.8 (C), 125.8 (2CH), 126.1 (CH), 126.3 (CH), 127.16 (2CH), 127.28 (4CH), 139.3 (C), 143.7 (C), 154.6 (C). Amine **5-62** (or **5-63**): R_f = 0.40 (100% EtOAc/hexanes); IR (neat) 3347, 2975, 1693 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 367.2386, found: 367.2351; $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 389.2205, found: 389.2204; ^1H NMR (500 MHz,

CDCl₃) δ 1.36 (s, 9H), 1.61-1.69 (m, 1H), 1.76-1.83 (m, 1H), 2.08 (pentet, $J = 9.3$ Hz, 1H), 2.13-2.20 (m, 1H), 2.76-2.83 (m, 1H), 2.87-2.95 (m, 2H), 3.25-3.30 (m, 1H), 3.53 (t, $J = 6.6$ Hz, 1H), 3.79 (t, $J = 8.2$ Hz, 1H), 4.70 (br, 1H), 6.85-6.94 (m, 4H), 6.95-7.00 (m, 4H), 7.16-7.30 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 24.6 (CH₂), 26.5 (3CH₃), 31.6 (CH₂), 35.6 (CH₂), 48.8 (CH₂), 66.7 (CH), 70.1 (CH), 77.0 (C), 124.6 (CH), 125.2 (CH), 125.3 (2CH), 125.54 (2CH), 125.62 (2CH), 126.8 (2CH), 137.1 (C), 141.4 (C), 153.9 (C). The following data were used to assign amines **5-62** and **5-63**.

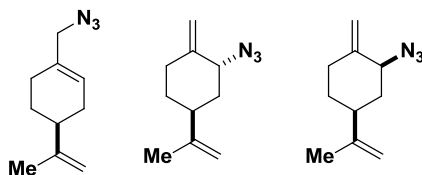


1-(Azidomethyl)-4-bromobenzene (5-20). To a solution of 4-bromobenzyl bromide (11.25 g, 45.00 mmol) in acetone (30 mL) and water (25 mL) was added sodium azide (8.8 g, 0.14 mol) portionwise. After the suspension was stirred overnight, diethyl ether and water were added. After separation, the aqueous layer was washed with diethyl ether three times.

The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (1-4% EtOAc/hexanes) to afford azide **5-20** (8.42 g, 88%) as a colorless oil. Azide **5-20**: R_f = 0.30 (100% hexanes); ^1H NMR (400 MHz, CDCl_3) δ 4.33 (s, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 54.1 (CH_2), 122.4 (C), 129.8 (CH), 132.0 (CH), 134.4 (C).

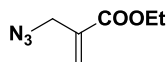


4-Bromo-*N*-methylenebenzenaminium trifluoromethanesulfonate (5-21). To a solution of azide **5-20** (145 mg, 0.684 mmol) in CD_2Cl_2 (1.5 mL) under N_2 atmosphere at 0 °C was added triflic acid (140 mg, 0.933 mmol) slowly. After the addition, ice bath was removed and the resulting green mixture was continued to stir for 20 min before NMR spectra were acquired. ^1H NMR (400 MHz, CD_2Cl_2) δ 7.62 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 8.26 (dd, J = 10.3, 7.0 Hz, 1H), 8.53 (dd, J = 17.2, 7.0 Hz, 1H), 14.38 (br, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 119.5 (q, J = 316 Hz, 1C), 122.7 (CH), 128.0 (C), 133.9 (CH), 134.3 (C), 161.2 (CH_2).



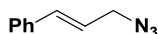
(*S*)-1-(Azidomethyl)-4-(prop-1-en-2-yl)cyclohex-1-ene (5-33), (2*R*,4*S*)-2-azido-1-methylene-4-(prop-1-en-2-yl)cyclohexane (5-34) and (2*S*,4*S*)-2-azido-1-methylene-4-(prop-1-en-2-yl)cyclohexane (5-35). Following the reported procedure,¹⁶⁹ to a solution of (*S*)-(-)-perillyl alcohol (6.1 g, 40 mmol) in Et_2O (50 mL) under N_2 atmosphere at 0 °C was

added DBU (7.31 g, 48 mmol) and diphenyl phosphoryl azide (13.21 g, 48 mmol). After allowing to warm to room temperature overnight, the precipitate was filtered and washed three times with pentane. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography (100% hexanes) to afford an inseparable mixture of azide **5-33**, **5-34**, and **5-35** (1:0.11:0.17 ratio, 3.6 mg, 51%) as a colorless liquid. Allylic azide **5-33**, **5-34**, and **5-35**: $R_f = 0.25$ (100% hexanes); IR (neat) 2922, 2094 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{20}\text{H}_{31}\text{N}_6$ (2M+H) $^+$ 355.2610, found: 355.2613. Azide **5-33**: ^1H NMR (400 MHz, CDCl_3) δ 1.27-1.35 (m, 1H), 1.50-1.60 (m, 1H), 1.77 (s, 3H), 1.85-1.93 (m, 1H), 1.97-2.08 (m, 1H), 2.09-2.25 (m, 3H), 3.63-3.73 (m, 2H), 4.73-4.75 (m, 1H), 4.75-4.78 (m, 1H), 5.77 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 20.8 (CH_3), 27.1 (CH_2), 27.3 (CH_2), 30.5 (CH_2), 40.7 (CH), 57.4 (CH_2), 108.9 (CH_2), 126.4 (CH), 132.2 (C), 149.3 (C). Azide **5-34** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.73 (s, 3H), 4.25 (t, $J = 3.1$ Hz, 1H), 4.71 (br, 1H), 4.92 (br, 1H), 4.97 (br, 1H). Azide **5-35** (diagnostic peaks only): ^1H NMR (400 MHz, CDCl_3) δ 1.75 (s, 3H), 3.87 (dm, $J = 12.0$ Hz, 1H), 4.87 (br, 0H), 5.01 (br, 1H). Azides **5-34** and **5-35** (diagnostic peaks only): ^{13}C NMR (100 MHz, CDCl_3) δ 63.1 (CH), 64.8 (CH), 106.9 (CH_2), 109.2 (CH_2), 109.6 (CH_2), 112.6 (CH_2), 144.4 (C), 145.8 (C), 148.0 (C), 148.8 (C).



Ethyl 2-(azidomethyl)acrylate (5-31). To a suspension of ethyl 2-(hydroxymethyl)acrylate (430 mg, 3.30 mmol), PPh_3 (1.74 g, 6.62 mmol), and $\text{Zn}(\text{N}_3)_2 \cdot 2\text{Pyr}$ (760 mg, 2.48 mmol) in benzene (20 mL) at 0 $^\circ\text{C}$ under N_2 atmosphere was slowly added DEAD (2.88 g, 40% in toluene, 6.62 mmol). The resulting mixture was heated to reflux for 20 h. The reaction was cooled to rt and the solvent was removed in vacuo. The residue was

purified by chromatography (1-5% EtOAc/hexanes) to afford azide **5-31** (86 mg, 17%) as a colorless oil. Azide **5-31** : R_f = 0.30 (5% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 1.35 (t, J = 7.1 Hz, 3H), 4.08 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 5.86 (q, J = 1.2 Hz, 1H), 6.37-6.45 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.2 (CH_3), 51.5 (CH_2), 61.2 (CH_2), 127.8 (CH_2), 135.3 (C), 165.4 (C).



(E)-(3-Azidoprop-1-en-1-yl)benzene (5-29). A suspension of (*E*)-(3-bromoprop-1-en-1-yl)benzene (7.8 g, 40 mmol) and sodium azide (7.8 g, 0.12 mol) in DMF (60 mL) at room temperature was stirred overnight, before diethyl ether and water were added. After separation, the aqueous layer was washed with diethyl ether three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography (1-5% EtOAc/hexanes) to afford azide **5-29** (6.2 g, 97%) as a colorless oil. Azide **5-29**: R_f = 0.40 (5% EtOAc/hexanes); IR (neat): 3028, 2100 cm^{-1} ; HRMS (ESI) m/z calculated for $\text{C}_{18}\text{H}_{19}\text{N}_3$ ($2\text{M}+\text{H}^+$) 319.1671, found: 319.1670; ^1H NMR (400 MHz, CD_2Cl_2) δ 4.01 (dd, J = 0.8 Hz, 6.4 Hz, 1H), 6.33 (dt, J = 6.4 Hz, 16.0 Hz, 1H), 6.73 (d, J = 16.0 Hz, 1H), 7.33-7.51 (m, 5H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 53.0 (CH_2), 122.7 (CH), 126.6 (CH), 128.2 (CH), 128.7 (CH), 134.3 (CH), 136.2 (CH).

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